University of Alberta

General Solid-Phase Approach to the Synthesis of Chiral Triazacycloalkane Ligands with Stereogenic Backbone Substituents

By

Daniel S. Kopac

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

Department of Chemistry

Edmonton, Alberta

Fall, 2002

National Library of Canada
Acquisitions and Bibliographic Services
395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque nationale du Canada
Acquisitions et services bibliographiques
395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-81422-X

Canada

University of Alberta

Library Release Form

Name of Author: Daniel S. Kopac

Title of Thesis: General Solid-Phase Approach to the Synthesis of Chiral Triazacycloalkane Ligands with Stereogenic Backbone Substituents

Degree: Master of Science

Year Degree Granted: 2002

Permission is hereby granted to the University of Alberta Library to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly, or scientific research purposes only.

The author reserves all other publication and other rights in association with the copyright in the thesis, and except as herein before provided, neither the thesis nor any substantial portion thereof may be printed or otherwise reproduced in any material form whatever without the author's prior written consent.

permanent address:
#14-366 Wonderland Rd.S.
London, ON, Canada
N6K 1L4

May 30 / 2002

University of Alberta

Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled 'General Solid-Phase Approach to the Synthesis of Chiral Triazacycloalkane Ligands with Stereogenic Backbone Substituents' by Daniel S. Kopac in partial fulfillment of the requirements for the degree of Master of Science

Dr. Dennis G. Hall

Dr. Rik R. Tykwinski

Dr. Andrew M. MacMillan

Date approved by committee: May 30, 2002

ABSTRACT

The synthesis of triazacycloalkane derivatives with stereogenic centers has long been a desirable goal since it is known that these compounds promote the epoxidation of olefins in the presence of Mn (II) using H_2O_2 as the oxidant. Additionally, metal complexes of these ligands have been used as mimics of redox metalloenzymes, and for the non-oxidative cleavage of RNA and DNA. However, almost all of the work currently in the literature focuses on derivatization of these species at the nitrogen centers. This thesis shows that for the first time stereogenic versatility can be built into the carbon backbone of the triazacycloalkane. This work focuses on the synthesis of novel backbone-chiral triazacyclononanes and triazazcyclodecanes taking advantage of standard Fmoc-peptide chemistry and exhaustive amide reduction of the acylated dipeptides on solid-support. Subsequent cyclization of the resulting linear triamines is achieved via a double nucleophilic displacement of a bis-triflate tethering agent.

For Mom, Grandma Pajak, and in memory of Grandpa Pajak

I would like to thank professor Dennis Hall for his support, encouragement, and input throughout the duration of this project. His ideas were invaluable for the progress of this research.

I would like to thank the Hall group members, both past and present, for all their advice. In particular I would like to thank Michel for his friendship, ideas, and his love of good wine (and good beer). Dr. Hamid Hoveyda, thanks for the support when times seemed bleak (yo wassup!). I would like to thank Dave for his dry sense of humour that coincided so perfectly with mine. Thanks to Duane for sharing my passion for soccer and for proof-reading my thesis. Thanks to Jason for reading this document over, and for his ideas.

Thanks in particular to Nicky for putting up with me for as long as she has. Thanks to my mom and my family, for their prayers and their support, and for teaching me what it means to work for something.

I would like to thank the spectral services staff, especially Tom, for their advice on the characterization of the 'difficult' triazacycloalkane compounds.

I would like to thank the Natural Sciences and Engineering Research Council of Canada, the University of Alberta, and Dr. Hall for financial assistance throughout this program and this body of work.

TABLE OF CONTENTS

1. Introduction....1
1.1: The Polyamines....1
1.2: Macrocyclic Polyamines....5
1.3: Triazacyclononane (tacn) and Derivatives....9
1.4: Perspective and Objective of the Project....28
2. Solid-Phase Synthesis of Resin-Bound Oligoamines....30
2.1: Linker Synthesis....30
2.2: Synthesis of Resin-bound Polypeptides and Polyamines....34
2.3: Design and Synthesis of Solid-Support Immobilized Oligoamines as Precursors for the Chiral Derivatives of 1,4,7-tacn (**12**) and 1,4,7-tacd (**13**)....43
3. Synthesis of Polyazacycloalkanes....50
3.1: Initial Studies....50
3.2: Synthesis of Triazacyclononane **163**....63
3.3: Synthesis of triazacyclononane **168**....66
3.4: Synthesis of Triazacyclononane **172**....68
3.5: Synthesis of Triazacyclononane **175**....75
3.6: Synthesis of Triazacyclononane **189**....80
3.7: Synthesis of Triazacyclononane **196**....85
3.8: Synthesis of Triazacyclodecane **202**....88
3.9: Synthesis of Triazacyclodecane **207**....90
3.10: Synthesis of Triazacyclodecane **210**....92
3.11: Future Directions....93
3.12: Summary and Conclusions....97
4. Experimental Section....101
4.1: General....101
4.2: Linker Synthesis....107
4.3: Synthesis of Tripeptides....109
4.4: Synthesis of Oligoamines....121
4.5: Synthesis of Azacycloalkanes....135
4.6: Epoxidation Studies....145
4.7: Richman-Atkins Approach....150
Bibliography:....157
APPENDIX OF SELECTED SPECTRA....162

LIST OF TABLES

Table 2.1: Reduction protocol modification 38
Table 2.2: Table of Tripeptides **134** and Oligoamines **135** 48
Table 3.1: Reaction conditions attempted with ligand **149** 57
Table 3.2: Metal binding and styrene epoxidation conditions with ligand **154** 60
Table 3.3: Styrene epoxidation conditions using ligand **159** 61
Table 3.4: Styrene epoxidation experiments with ligands **167**, **168**, and **169** 68
Table 3.5: Styrene epoxidation conditions using ligands **170**, **171**, and **172** 70

LIST OF FIGURES

Figure 1. 1: spermine (**1**), spermidine (**2**), putrescine (**3**) 1
Figure 1. 2: philanthotoxin-433 (**4**) 2
Figure 1. 3: valinomycin 6
Figure 1. 4: nitrogen macrocyle 6
Figure 1. 5: macrocyclic polyamines 6-11 and the increasing trend of Cu(II) binding 7
Figure 1. 6: 1,4,7-triazacyclononane (**12**) and
1,4,7-trimethyl-1,4,7-triazacyclononane(**13**) 9
Figure 1. 7: triazamacrocycle **23** and tetrazamacrocycle **24** 13
Figure 1. 8: cooperativity model for ApA with a binuclear Cu(II) complex 14
Figure 1. 9: heptapeptide **25** incorporating two Zn(II)-tacn side chains 15
Figure 1. 10: cooperativity mechanism for heptapeptide **25** 16
Figure 1, 11: mono-nuclear Zn(II)-tacn pentapeptide **26** 17
Figure 1. 12: preparation of azamacrocycles by the Richman-Atkins protocol 18
Figure 1. 13: Richman-Atkins protocol to triazacyclononane **38** 19
Figure 1. 14: dmtacn, 58, and its derivative, **59** 23
Figure 1. 15: general structure of chiral macrocyclic polyamines 29
Figure 2. 1: tritylchloride polystyrene (PS-Trt-Cl) 30
Figure 2. 2: 1,8-diaminooctane linker **86** and cross-linked species **85** 34
Figure 2. 3: coupling reagents 35
Figure 2. 4: structures of putative *N,N*-acetals 41
Figure 2. 5: reduction of tripeptide **131** 47
Figure 3. 1: resin bound tetramine **105** 52
Figure 3. 2: Dde-protected triazacyclononane **165** 65
Figure 3. 3: piperazinium ion **166** 66
Figure 3. 4: triazacyclononane **168** and derivative **169** 67
Figure 3. 5: piperazinium ion **173** 69
Figure 3. 6: piperazinium ion **176** 76
Figure 3. 7: ES-MS fragments **177** and **178** 77
Figure 3. 8: piperazinium ion **179** 77
Figure 3. 9: ES-MS fragments **191** and **192** 81
Figure 3. 10: possible piperazinium adduct **193** 81

Figure 3. 11: LC-MS of **190** and **193** 84
Figure 3. 12: piperazinium ion **197** 86
Figure 3. 13: LC-UV-MS of **196** 87
Figure 3. 14: structures and ratios of triazacyclononanes (**198**, **199**, **200**) to the corresponding piperazinium ions 88
Figure 3. 15: piperazinium ion **208** 91
Figure 3. 16: Piperazinium ion **211** 92

LIST OF SCHEMES

Scheme 1. 1 2
Scheme 1. 2 5
Scheme 1. 3 10
Scheme 1. 4 12
Scheme 1. 6 18
Scheme 1. 7 20
Scheme 1. 8 21
Scheme 1. 9 22
Scheme 1. 10 23
Scheme 1. 11 24
Scheme 1. 12 25
Scheme 1. 13 26
Scheme 1. 14 27
Scheme 1. 15 28
Scheme 1. 16 29
Scheme 2. 1 31
Scheme 2. 2 33
Scheme 2. 3 34
Scheme 2. 4 36
Scheme 2. 5 37
Scheme 2. 6 39
Scheme 2. 7 40
Scheme 2. 8 41
Scheme 2. 9 43
Scheme 2. 10 45
Scheme 2. 11 46
Scheme 2. 12 48
Scheme 2. 13 49
Scheme 3. 1 50
Scheme 3. 2 52
Scheme 3. 3 53
Scheme 3. 4 53

Scheme 3. 5 54
Scheme 3. 6 55
Scheme 3. 7 56
Scheme 3. 8 57
Scheme 3. 9 59
Scheme 3. 10 61
Scheme 3. 11 63
Scheme 3. 12 64
Scheme 3. 13 67
Scheme 3. 14 69
Scheme 3. 15 71
Scheme 3. 16 72
Scheme 3. 17 74
Scheme 3. 18 74
Scheme 3. 19 75
Scheme 3. 20 78
Scheme 3. 21 79
Scheme 3. 22 80
Scheme 3. 23 82
Scheme 3. 24 83
Scheme 3. 25 86
Scheme 3. 26 89
Scheme 3. 27 90
Scheme 3. 28 91
Scheme 3. 29 92
Scheme 3. 30 94
Scheme 3. 31 96

LIST OF ABBREVIATIONS

AcOH	acetic acid
Ac_2O	acetic anhydride
ADP	adenosine diphosphate
AMP	adenosine monophosphate
ApA	adenosine-phosphate-adenosine
APT	attached proton test
ATP	adenosine triphosphate
BB	broad band
BOC	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxy-*tris*(dimethylamino)phosphonium hexafluorophosphate
°C	degree Celcius
^{13}C NMR	carbon-13 magnetic resonance
calcd.	calculated
cAMP	cyclic adenosine monophosphate
CBZCl	carbobenzyloxy chloride
CD_3OD	deuterated methanol
δ	chemical shift downfield from TMS
d	doublet
dd	doublet of doublets
DAD	diode array detector
DCM	dichloromethane
Dde	1-(4,4-dimethyl-2,6-dicyclohexylidene)ethyl
DEPT	distortionless enhancement by polarization tranfer
DIC	2-(dimethylamino)isopropyl chloride hydrochloride
DIPEA (DIEA)	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
dmtacn	1,4-dimethyl-1,4,7-triazacyclononane
DNA	2′-deoxyribonucleic acid

equiv.	equivalents
ES-MS	electrospray mass spectrometry
ESR	electron spin resonance
Fmoc	9-fluorenylmethoxycarbonyl
Fmoc-D-Ala-OH	*N*-α-Fmoc-D-alanine
Fmoc-D-Leu-OH	*N*-α-Fmoc-D-leucine
Fmoc-D-Phe-OH	*N*-α-Fmoc-D-phenylalanine
Fmoc-Gly-OH	*N*-α-Fmoc-glycine
Fmoc-L-N-Me-Ala-OH	*N*-α-Fmoc-*N*-α-methyl-L-alanine
Fmoc-L-N-Me-Leu-OH	*N*-α-Fmoc-N-α-methyl-L-leucine
Fmoc-L-N-Me-Phe-OH	*N*-α-Fmoc-N-α-methyl-L-phenylalanine
Fmoc-L-Pro-OH	*N*-α-Fmoc-L-proline
Fmoc-N-Me-Gly-OH	*N*-α-Fmoc-sarcosine
h	hours
^{1}H NMR	proton magnetic resonance
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HBTU	*O*-Benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HIV	human immunodefficiency virus
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HOBt	1-Hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
J	coupling constant
LC-MS-UV	liquid chromatography-mass spectrometry-ultraviolet spectroscopy
m	multiplet
Me	methyl
MeCN	acetonitrile

MeOH	methanol
min.	minutes
MSD	mass spectroscopic detector
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
nosyl-Cl	2-nitrobenzenesulfonyl chloride
PMB	*para*-methoxybenzyl
PP	polypropylene
ppm	parts per million
PS	polystyrene
PS-DIEA	polystyrene diisopropylethylamine
p-TsOH	*para*-toluene sulfonic acid
PyBrOP	bromotris(pyrolidino) phosphonium hexafluorophosphate
quart.	quartet
quint.	quintet
RNA	ribonucleic acid
r.t.	room temperature
Rt	retention time
s	singlet
SES-sulfonamides	β-trimethylsilylethanesulfonyl
t	triplet
tacn	1,4,7-triazacyclononane
*t*BuOLi	lithium *tert*-butoxide
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
tmtacn	1,4,7-trimethyl-1,4,7-triazacyclononane
Triflic anhydride	trifluoromethanesulfonic anhydride
TrtCl	tritylchloride
Ts	*para*-toluenesulfonate
UV	ultraviolet

1. Introduction

1.1: The Polyamines

1.1.1: Naturally Occurring Linear Polyamines[1]

As early as 1677 Anton von Leeuwenhoek discovered a crystalline substance from human seminal fluid that was later determined to be spermine phosphate, the salt of a natural occurring polyamine. Polyamines, such as the ubiquitous species spermine **1** (1,12-diamino-4,9-diazadodecane), spermidine **2** (1,8-diamino-4-azaoctane) and their precursor putrescine **3** (1,4-diaminobutane), are low molecular weight components of almost every type of prokaryotic and eukaryotic cell (Figure 1.1). [2,3]

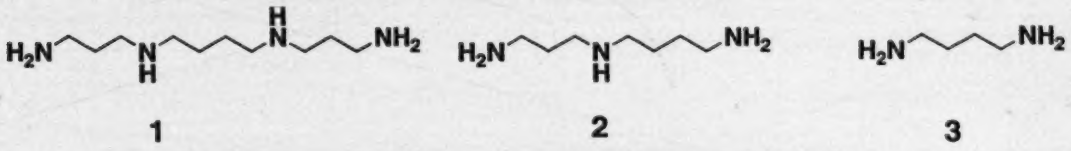
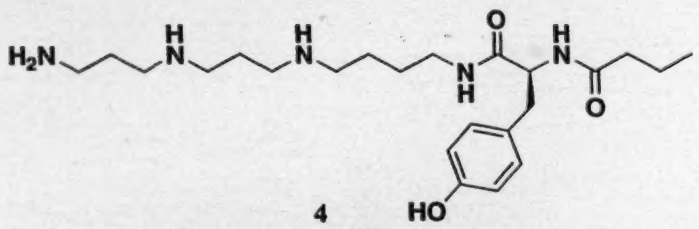


Figure 1. 1: spermine (1), spermidine (2), putrescine (3)

Synthetic derivatives of these naturally occurring polycations have potential uses in the treatment of disorders such as cancer (rapidly dividing cancer cells are known to have a high demand for polyamines), parasitic infections, as well as their potential use as ion-channel blockers or vectors in gene delivery.[4] In addition, it has also been shown that these compounds hold promise as antimalarials, antidiarrhoeals, and anti-HIV agents.

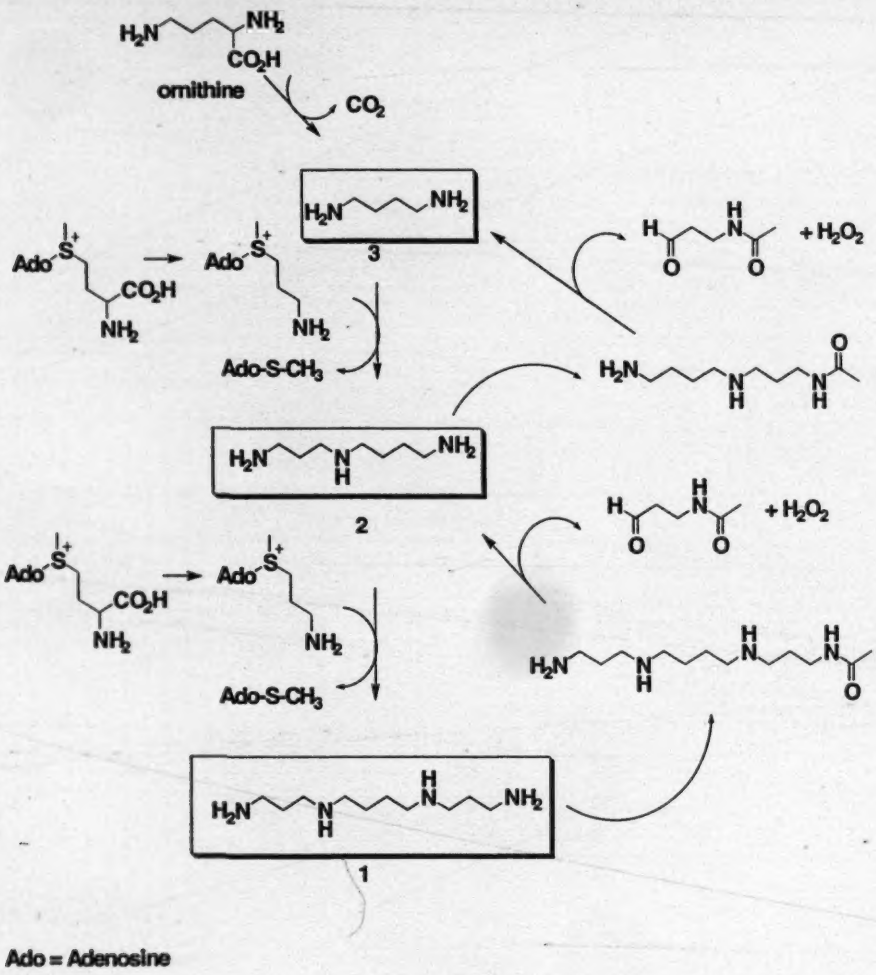
Additionally, polyamines have been found as components of venoms and toxins produced by a number of organisms. In 1957 one of the first polyamine toxins to be identified was that of tarantula spiders, whose venom targets specific neuromuscular junctions found in their insect prey.[5] The venom of the parasitic digger wasp, *Philanthus triangulum*, contains several low molecular weight neuroactive compounds, of which philanthotoxin-433 (**4**, Figure 1.2) is the primary constituent.



4

Figure 1. 2: philanthotoxin-433 (4)

The endogenic polyamines spermidine (**1**), spermine (**2**), and putrescine (**3**) are involved in a variety of biological functions in mammals. Their biosynthetic origin *in vivo* can be traced to L-Ornithine, L-Arginine, and L-Methionine(Scheme 1.1).[6]



Scheme 1. 1

The predominant pathway of their synthesis involves the stepwise transfer of γ-aminopropyl groups to putrescine (**3**), forming the desired polyamine chain length. The regulation of the concentration of these polyamines in cells largely depends on the enzymes involved in their synthesis and their transport through cell membranes (efflux). The transport systems in cells (active transport) is permissive enough that it allows for a variety of synthetic polyamines, and their derivatives and analogues, to use it.

The above metabolic pathways of the endogenous polyamines have been elucidated for a few organisms. Their biological significance, however, is only fully appreciated with the realization that they interact strongly with nucleic acids and play an important role in nucleic acid biosynthesis and metabolism. The polycationic nature of these polyamines, in organisms, is greatly stabilized because of their interaction with the negatively charged phosphate groups of the DNA backbone. An interesting consequence of this phenomenon is that these polycationic species are able to form bridges between two different molecules of DNA and thereby induce changes in the DNA structure.[7] This property, as well as the previously mentioned ones, makes polyamines a target of particular importance in synthetic organic chemistry.

1.1.2: Solution Phase Synthesis of Polyamines

A number of solution-phase syntheses of polyamines have been reported and the subject has been extensively reviewed. [7-9] There are a number of preparative methods for polyamines but the details will not be presented here. In general, the syntheses of polyamines are long and tedious, relying on extensive iterative protection and deprotection of the amino groups, and require time-consuming separations and purifications of the product mixtures. There is also a need for the development of methodology to be able to modify these amines and extend their chain length.

At the root of the problem is the linear strategy involved in forming these amines, in which masked diamine building blocks are individually added to nitrogen containing functionalities. Efficient transfer of these solution phase methods to solid-phase synthesis would considerably simplify these efforts. In particular, a convergent strategy based on established solid-phase methods to access polypeptides and their exhaustive

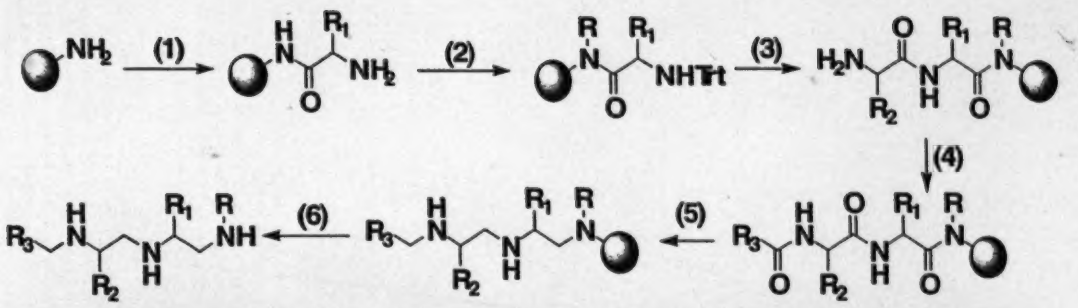
reduction to yield polyamines is highly desirable. In addition, such a solid-phase approach would allow for the inclusion of chiral side chains derived from α-amino acids.

1.1.3: Solid-Phase Synthesis of Polyamines

In 1963, Merrifield demonstrated the first proof of concept for the synthesis of peptides on solid support[10] that later helped to lay the foundation for the field of combinatorial chemistry. The main advantage of combinatorial chemistry is that it allows for the rapid synthesis and screening of compounds. Solid-phase chemistry permits immobilization of substrates or reagents on a solid matrix, allowing them to be chemically manipulated. The benefit is that large excesses of reagents can be used to drive the reactions to completion and the often laborious steps of purification are not required. The objective is to effect the desired transformation without the premature release of the substrate from the support. Thus, methodology research encompasses the development of protocols that are suited for the characteristics of a particular solid-support enabling high control over conditions that will liberate the substrate.

The synthesis of polypeptides on solid support follows very well established chemistry. First, it starts with attaching a suitable linker to the support, followed by a coupling of the appropriately protected amino acid based on traditional amide formation chemistry. By deprotecting the amino acid residue and repeating the coupling cycle a peptide can be 'grown' to the desired size, often in high yield and purity.

Due to the appealing intrinsic advantages of solid-phase organic synthesis (SPOS), there is enormous interest in the development of such methods to facilitate the synthesis of polyamine derivatives. Houghten, amongst others, has shown that it is possible to exhaustively reduce *N*-acylated peptides on solid support to provide amines (Scheme 1.2).[11]



(1) (a) Boc-Xaa-OH; (b) 55% TFA/DCM (2) (a) TrtCl, DIPEA, DCM; (b) RX, *t*BuOLi, DMSO (3) (a) 2% TFA/DCM; (b) DIPEA/DCM; (c) Fmoc-Xaa-OH; (d) 20% piperidine/DMF (4) R_3COOH, DIC, DMF (5) BH_3/THF (6) HF/anisole

Scheme 1. 2

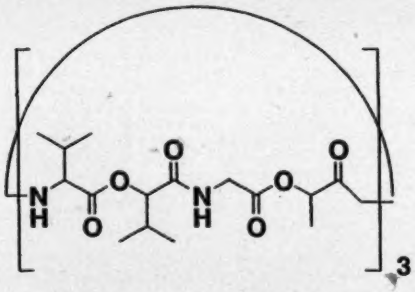
Recently our group published an improved synthesis of polyamines on solid-support.[12] We describe the use of practical trityl-based resin linkers for the synthesis of chiral polyamines. These are derived from the exhaustive reduction of *N*-acetylated polypeptides containing diverse side-chain functionalities that originate from α-amino acids. Our methodology for the liberation of the free amines uses a buffered iodine solution (acetic acid-acetate) with the main advantages being that no heating is required and the use of strong acids or bases is not necessary so that the premature release of substrate from the solid support is avoided.

1.2: Macrocyclic Polyamines

1.2.1: Development of Macrocyclic Polyamines

With the discovery and characterization of the ionophore valinomycin (Figure 1.3)[13], a cyclic compound that affects the transport of certain cations, efforts have been focused on the isolation and development of other compounds possessing similar biological properties. In the late 1960's Lehn and collaborators, taking note of the chemical reactivity of valinomycin and the more stable crown ethers, began a program to develop compounds with internal cavities that may complex guests even stronger than valinomycin. They found that macrobicyclic ligands containing secondary nitrogen and

oxygen ethers encompassed the desired properties. These new structures, for example, could bind an ammonium cation much more strongly than crown ethers could.

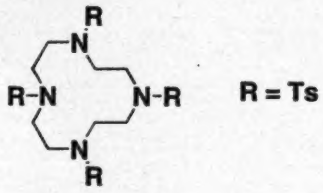


L-Val-D-Hydroxyisovaleric acid-D-Val-L-Lactic Acid

Figure 1. 3: valinomycin

The subsequent 'cryptands' were macrotricyclic and became tailored so as to increase their efficiency at binding one molecule selectively over another (e.g. RNH_3^+, H_2O, Cl^-). Lehn considered these macrocycles as receptors and generalized the possibility of developing interacting structures that could mimic and extend biological function.

Early in the development of macrocyclic chemistry it was noted that the nitrogen containing macrocycles had an enhanced selectivity for potassium over sodium. This observation soon led to the synthesis of nitrogen macrocycles linked entirely through their nitrogen atoms.[14] The synthesis of these compounds was centered on a reaction between a bis-sulfonamide sodium salt and sulfonate ester leaving group to give compounds such as **5** (Figure 1.4).



5

Figure 1. 4: nitrogen macrocyle

Initially it was noted that attempts at synthesizing macrocycles incorporating hydrocarbon residues of more than three methylene groups led to reduced yields. Improvements to the synthesis by Richman and Atkins have been reported (see below).

In 1989 McMurry demonstrated the design and synthesis of macrocyclic ligands aimed at optimizing the binding of specific metals.[15] To this end, a series of polyamine ligands were synthesized in which the cavity size was progressively increased and the binding of cations such as Cu(II) was investigated in relation to the linear polyamine counterpart. It was found that the linear and cyclic polyamines bound the cations with similar rates in the unprotonated form, however, the protonated macrocyclic ligands react more slowly than their linear analogues. Within the series of macrocyclic polyamines (**6-11**), the binding rate constant increases with increasing ring size with Cu(II) as the cation (Figure 1.5).

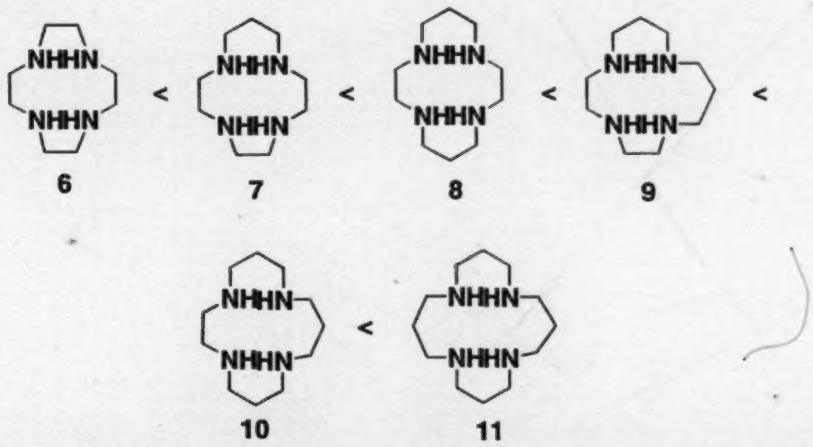


Figure 1. 5: macrocyclic polyamines 6-11 and the increasing trend of Cu(II) binding

Thus macrocyclic polyamines possessing 5 or 6 nitrogen atoms and having 15 or 16 members in the ring can effectively bind ions such as Cu(II) or the divalent transition metals. In fact these pentaazamacrocycles of 15 and 16 members were found to bind Cu(II) 10^4-10^5 times stronger than the related linear structures which lack a linking di- or tri-methylene bridge. This enhanced binding has been termed 'the macrocyclic effect', and has also been observed in the tetraaza and triaza compounds. Related to this work, Hori has calculated the relationship between the number of atoms in the rings of the

macrocycles and the cavity size.[16] Thummel has also provided a summary of the syntheses of polyazamacrocycles with different cavity sizes.[17]

The uses of these macrocyclic polyamines are quite varied. They have been demonstrated to act as selective receptor molecules for polyoxyanions such as succinate and citrate, intermediates in the citric acid cycle. This receptor ability occurred at physiological pH.

Macrocycles that bear an intraannular phenolic group were found to specifically bind divalent metals such as Mg(II) specifically. Those bearing a pyridine sidearm are specific for Na(I). As such it was possible to develop functionalized macrocyclic polyamines that could selectively bind the alkali-metals.[18] Consequently, this observation led into new areas of research, dealing with the analytical and medicinal applications of these macrocyclic polyamines. One potential application of these complexes is as agents capable of complexing an antibody that can be used to target radioactive metal complexes, and thus providing a potential use for diagnosis or therapy.

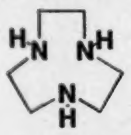
Other biological properties of these compounds includes stimulation of poly C RNase A, slight inhibition of ATPase in contrast to a high inhibition by spermine, and a large inhibitory affect of lipid peroxidation due to chelation of Fe(II). A lanthanum complex of a macrocyclic polyamine that contained an acetamide substituent on the nitrogen was found by Amin to be a stable catalyst active in the rapid cleavage of RNA oligomers.[19] Furthermore, the binding of the macrocyclic polyamines to ATP and other phosphoanhydrides revealed some surprises. In their protonated form these compounds bind ATP, ADP, and AMP strongly. They also enhance the rate of hydrolysis of ATP over a wide pH range by several orders of magnitude as compared with a linear hexamine that does bind ATP but does not increase the rate of hydrolysis. As a result, these macrocyclic polyamines have been described as 'functional mimics' of ATPases.[20] Other applications of macrocyclic polyamine ligands include photosensitizers in solar cells, catalysts for organic transformations, mimics of redox metalloenzymes, and mimics of hydrolytic enzymes.

It is as a result of all these features that this class of molecules constitutes a particularly attractive target for organic synthesis.

1.3: Triazacyclononane (tacn) and Derivatives

1.3.1: Development and Applications

Amongst all classes of macrocyclic polyamines, 1,4,7-triazacyclononane (tacn, **12,** Figure 1.6) and its derivatives have received tremendous attention in recent years. This is especially true in the development of mimics of redox metalloenzymes, in the design of selective cleaving agents for RNA and DNA, and as well as in oxidation reactions such as the epoxidation of olefins. However, although these types of ligands are well known, their syntheses are not always trivial; for example, the cyclization reactions used to form them rely on the statistical formation of a complex mixture of desired product accompanied by oligomeric material. Also, the preparation of suitable open chain precursors can be very tedious.



tacn
12

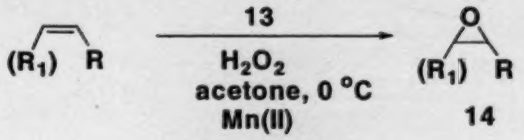
tmtacn
13

Figure 1. 6: 1,4,7-triazacyclononane (12) and 1,4,7-trimethyl-1,4,7-triazacyclononane(13)

The oxidation of olefins is able to generate synthetically useful intermediates. At the onset of this work, our interests were primarily with the development of these azacycloalkanes as efficient catalysts for the epoxidation of olefins. Industrially, epoxidations are often performed with stoichiometric reagents such as peracids, or using Payne's procedure that combines a nitrile with hydrogen peroxide producing a peroxycarboximidic acid.[21] Other epoxidation protocols are not feasible on an industrial scale because of the inherent toxicity issues associated with the reagents. Thus, considerable effort has been devoted to developing a 'green' alternative, using H_2O_2 instead of inorganic oxygen donors, avoiding halides or toxic metals, and making stable products at nearly neutral pH.

In 1994, a team of researchers from Unilever showed that manganese complexes of tacn were effective catalysts for the bleaching of stains by H_2O_2 at low temperatures.[22] In addition, they showed that these complexes also catalyzed the epoxidation of simple olefins.

In 1996, Bein investigated the effect of reaction conditions of the manganese complexes of tmtacn (1,4,7-trimethyl-1,4,7-triazacyclononane, **13**, Figure 1.6) on the proportion of undesired side reactions that accompany these types of epoxidations of olefins, namely oxidant disproportionation reactions.[23] He found that by choosing the appropriate reaction conditions, the balance between the desired epoxidation process and the disporportionation of the oxidant is shifted toward the former, thereby permitting the epoxidation of less reactive alkenes. Thus, the gradual addition of aqueous 30% H_2O_2, diluted in an organic solvent, to a mixture of olefins, Mn(II), and ligand, produced the desired catalytic reactions. It was found that the temperature and the solvent greatly affected the epoxidation, with low temperatures and acetone as the solvent providing the greatest catalyst turnover and rate of epoxide (**14**) formation (Scheme 1.3).



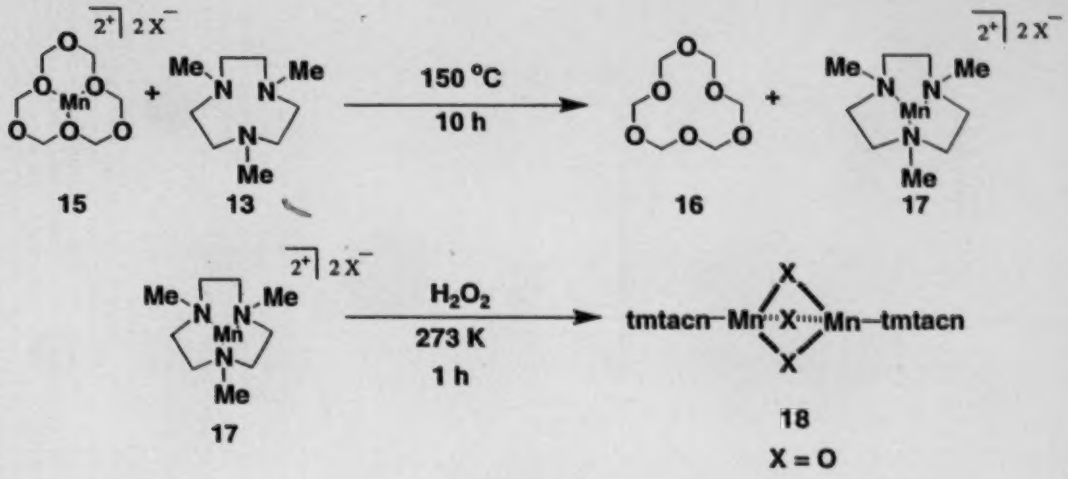
Scheme 1. 3

Interestingly, the use of alcoholic solvents proved to be partially responsible for the loss of the oxidant, due to solvent oxidation. Also, this group found that epoxide yields were greatly dependent on the counter anion in solution. With sulfate as the counter anion, the yields were approximately four times higher than those with chloride or perchlorate salts. Bein attributed these differences to the known effects of these anions on the oxidative chemistry of Mn(II) and tmtacn. The proposition was that the bridging anions, such as sulfate or acetate, promote the *in situ* formation of oxidized manganese dimers that have been implicated in this chemistry. Furthermore, Bein observed such species through the use of X-band ESR spectroscopy. With the sulfate and acetate counter anions, a diagnostic 16-line signal of a Mn(III)-Mn(IV) dimer was observed, and

with the chloride and perchlorate systems only a 6-line signal diagnostic of a monomeric Mn(II) is dominant. The major product in these reactions was the epoxide, with the minor side reactions being the oxidative cleavage of the double bond in the styrene series or allylic oxidation in the alkenes.

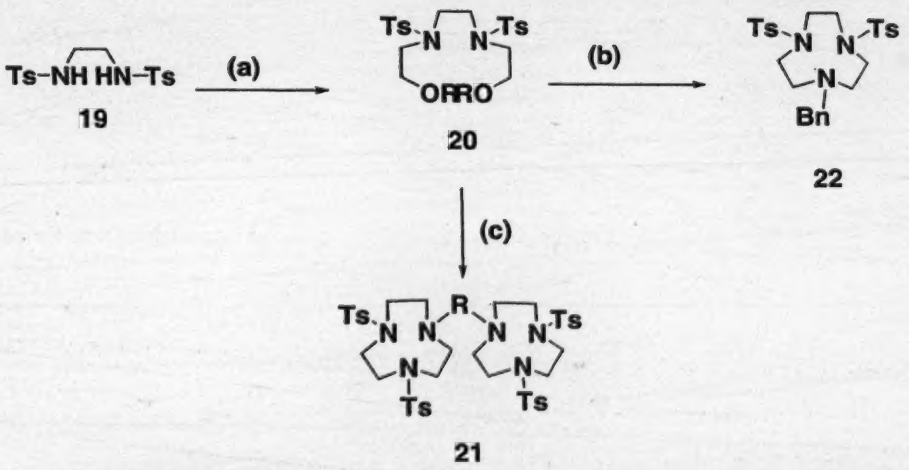
Bein's group also introduced tacn containing zeolites for use as epoxidation catalysts.[23,24] These catalysts were prepared by reacting a Mn(II)NaY zeolite **15**, with the cyclic triamine ligand **13**, for 10 h at 150° C under an inert atmosphere with occasional shaking (Scheme 1.4) to form monomeric compound **17**. In this system the combined effect of low temperature, gradual peroxide addition, and the use of acetone as solvent let to a marked decrease in oxidant disproportionation and an increase yield of epoxide by a factor of 50. In addition, solvolysis with this zeolite system is minimal.

Bein also observed that the structure of the tacn ligand was crucial for the selective epoxidation reaction. The unmethylated tacn **12** displayed a dramatic disproportion reaction with H_2O_2 and gave very low levels of olefin epoxidation. On the other hand, the methylated tmtacn analogue provided a well-suited environment for the epoxidation reaction. Bein has proposed that the methyl groups, in addition to serving a protective function against ligand oxidation, might also provide a hydrophobic wrapping around the manganese ion.[25] He suggested that this shielding effect favors the adsorption of an olefin at the peroxide-activated Mn(II) ion, which slows down the approach of subsequent peroxide molecules, preventing the decomposition of the oxidant. Furthermore, this zeolite system also displayed the characteristic 16-line X-band ESR signal that suggests the oxidative formation of the catalytic species as a mixture of Mn(III)-Mn(IV) dimer **18**.[25]



Scheme 1. 4

Recently, Watkinson and co-workers demonstrated that it is possible to make binucleating ligands incorporating two tacn derivatives. This is achieved by linking two of these groups *via* an ethylene tether, thus creating an intramolecular version of the binucleating ligand, analogous to **18**.[26] They employed an adapted procedure using K_2CO_3 as the base in DMF and subsequent cyclization of the tosylamide precursor **20** with either a diamine, to form the binucleating species (**21** below), or benzylamine to form a tacn derivative (**22**, see Scheme 1.5).



Reaction conditions: (a) (i) ethylene carbonate, K_2CO_3, DMF, 94% (ii) TsCl, Et_3N, DMAP (cat.), DCM (b) $BnNH_2$, CH_3CN, K_2CO_3, 5 days (c) $NH_2(R)NH_2$, CH_3CN, K_2CO_3

Scheme 1. 5

This reaction, involving both intramolecular and intermolecular steps with four nucleophilic displacements, was shown to proceed well with benzylic and aliphatic diamines, giving the products in high yield. Interestingly, the formation of the nine-membered ring was highly favoured when benzylamine was reacted with **20** (step b in Scheme 1.5) using K_2CO_3 in acetonitrile, while the binucleating species **21** was exclusively formed when using the conditions of an appropriate diamine with K_2CO_3 in acetonitrile (step c in scheme 1.5). The work of this group has been further extended to the formation of larger macrocyclic rings containing three and four nitrogen atoms using tosylamides or benzylamines.[27] The cyclization reactions with the tosylamides proved to work well for a 10-membered triaza-macrocycle **23** and the cyclen derivative **24** (Figure 1.7). However, the reaction did not work so well with the benzylamine, giving the desired product after chromatographic purification only in low yield.

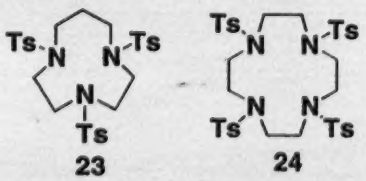


Figure 1. 7: triazamacrocycle 23 and tetrazamacrocycle 24

These types of binuclear complexes are not limited to oxidation reactions of olefins and related compounds. As demonstrated by Chin[28] in 1995, dinuclear Cu(II) complexes of the sort shown in Figure 1.8 have been used to cleave 2′,3′-cAMP and RNA, although the latter is not the most reactive metal complex reported for hydrolyzing RNA. However, this system does represent the first example of metal centers that cooperatively cleave the phosphate diester bonds of RNA and 2′,3′-cAMP. The authors propose that this cooperation is due to the bridging of the phosphate esters by the two metallic centers (Figure 1.8). It was also shown that as a result of this cooperativity, the binuclear complexes are about 500 times more reactive in the cleavage of ApA (Adenosine-phosphate-Adenosine) than the mononuclear Cu(II) complexes.

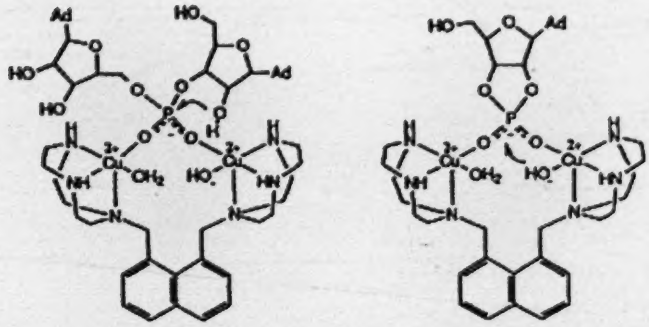
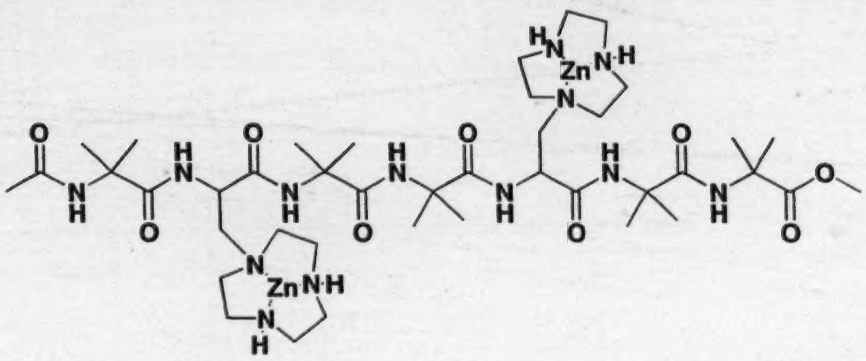


Figure 1. 8: cooperativity model for ApA with a binuclear Cu(II) complex[28]

Scrimin and co-workers also report a bimetallic transphosphorylation catalyst **25** active in water.[29] Their model is based on a helical heptapeptide, consisting of five copies of the α-carbon-tetrasubstituted α-aminoisobutyric acid, which was chosen for conferring a stable helical conformation on such a short peptide (Figure 1.9)



25

Figure 1. 9: heptapeptide 25 incorporating two Zn(II)-tacn side chains[29]

Their results indicated that each of the tacn side chains binds to a separate metal ion instead of sharing one metal ion. Studies of the intramolecular transesterification reaction of an RNA model substrate, 2-(hydroxypropyl)-*p*-nitrophenyl phosphate (HPNP), showed that the heptapeptide **25** demonstrates that the cooperativity of the two metal centers shows up to a 5-fold increase on the rate of reaction compared with the mononuclear complex.

A mechanism for the cooperativity effect has been proposed where the two metal centers each bind the substrate in a way that confers the appropriate reactivity at each center (Figure 1.10).

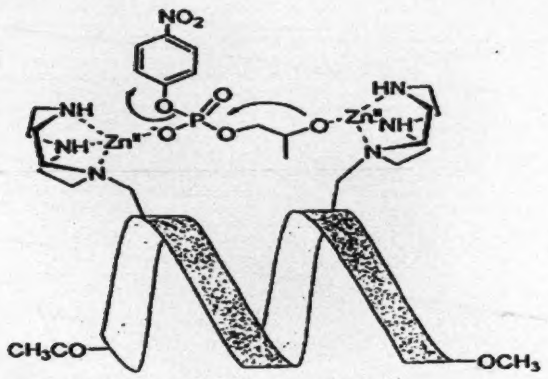
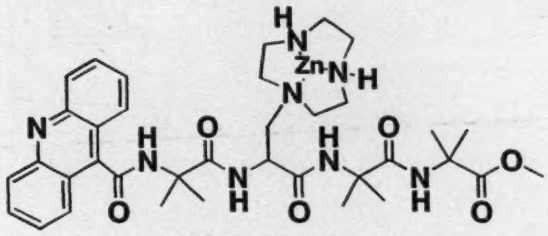


Figure 1. 10: cooperativity mechanism for heptapeptide 25

However, when this heptapeptide was tested with the DNA model substrate bis-*p*-nitrophenyl phosphate, no evidence was produced for the acceleration of cleavage. Nevertheless, it was argued that polyanionic DNA would have enhanced interactions with the metal centers and so could be an accessible hydrolytic target. Indeed, dinuclear complexes of Zn(II) with the heptapeptide ligands showed a remarkable activity for the cleavage of plasmid DNA that pointed to the cooperativity between the two metal centers.[30] When plasmid DNA was incubated at 37 °C for 24 h in 20 mM HEPES buffer at pH 7 in the presence of the metal-ligand complex **25**, it was converted from supercoiled form, to both nicked and linear form, which was exactly dependent on the concentration of the dinuclear complex. Compared with the mononuclear complex **26** (Figure 1.11), the dinuclear complex **25** was more than 20 times more active in the hydrolytic cleavage. Although the heptapeptide **25** has shown promise, as yet structural variation has remained unexplored because of the difficulty of their synthesis.



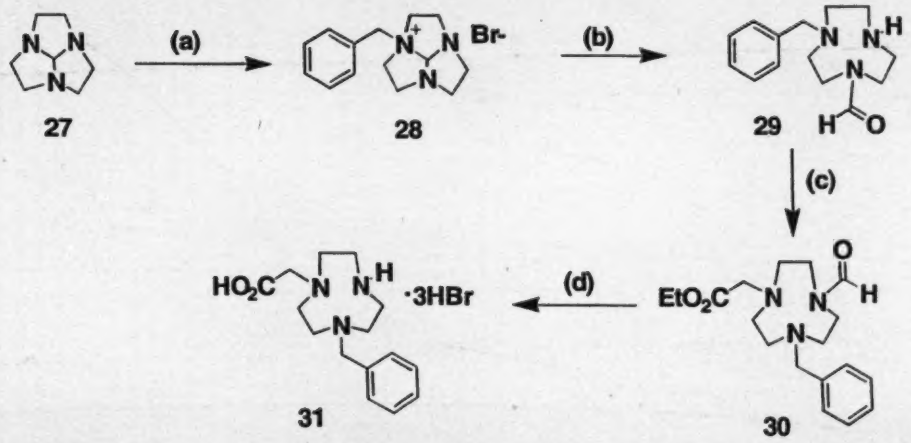
26

Figure 1. 11: mono-nuclear Zn(II)-tacn pentapeptide 26

1.3.2: Synthesis of tacn, tacn-derivatives and their use in Epoxidation Reactions of Olefins.

The highly favoured method for the formation of tacn and its derivatives has been to modify the existing 1,4,7-triazacyclononane core on the secondary nitrogen centers to yield functionalized macrocycles with pendant side-groups. Indeed, there have been extensive reviews of the subject in the literature.[31] The common feature of these syntheses is their rather straightforward approach, as they all involve the attachment of three identical groups to the secondary nitrogen atoms.

A recent synthesis is worthy of note, performed by Spiccia and co-workers, because it yields unsymmetrically substituted derivatives of 1,4,7-triazacyclononane. The key to this transformation is the use of 1,4,7-triazatricyclo[5.2.1.0]decane **27** (tacn orthoamide), which itself was prepared by refluxing 1,4,7-triazacyclononane **12** with 1 equivalent of dimethylformamide dimethylacetal in toluene. This derivative was subsequently reacted as shown in Scheme 6 to yield the unsymmetrical tacn derivatives in good to moderate yields.[32]



(a) $BrCH_2Ph$/THF; (b) H_2O; (c) $BrCH_2CO_2Et/Na_2CO_3$/MeCN; (d) (i) 5M HCl, (ii) CH_3COOH/HBr(g)

Scheme 1. 6

One of the first reported methods for making the nitrogen macrocycles was based on the condensation of terminal dihalides with bis-sulfonamide sodium salts under high dilution conditions. In 1972 Koyama and Yoshino reported a synthesis of a trisulfonamide derivative of both tacn **12** and 1,4,7-triazacyclodecane.[33] Richman and Atkins found in 1974 that using preformed bis-sulfonamide sodium salts with sulfonate esters, as leaving groups, in a dipolar aprotic solvent, allowed for the large-scale preparations of the macrocycles (Figure 1.12).[14]

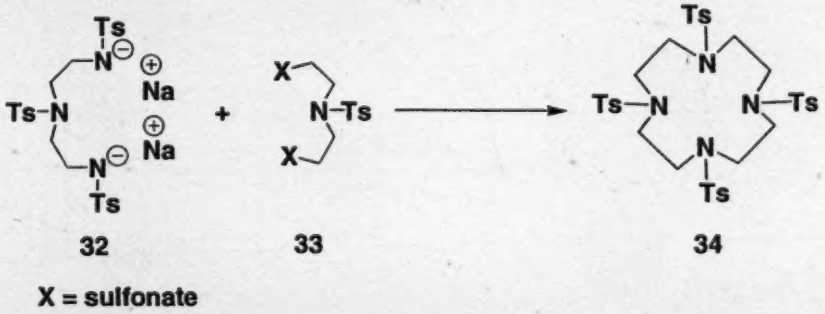


Figure 1. 12: preparation of azamacrocycles by the Richman-Atkins protocol

Subsequently, cyclic polyamines were usually synthesized using the Richman-Atkins protocol for a few reasons. Firstly, the sodium salts have an enhanced nucleophilicity over the tosylated amines. Secondly, the sulfonate esters are more effective leaving groups than the halides used in previous methods. Thirdly, high-dilution

conditions and extended reaction times are not necessary for enhanced yields. When using this protocol the bis-sodium salt **35** of the tosylamide is formed *in situ* and reacted with the bis-tosylate **36** to form the desired macrocycle **38.**[34] In principle, intermediate **37** (Figure 1.13) could further react with either a bistosylate or a tosylamide. However, the authors found only trace amounts of the products corresponding to varying ratios of **35** to **36** incorporation in the macrocycle (such as 2:1, 1:2, and 2:2 **35**:**36**).

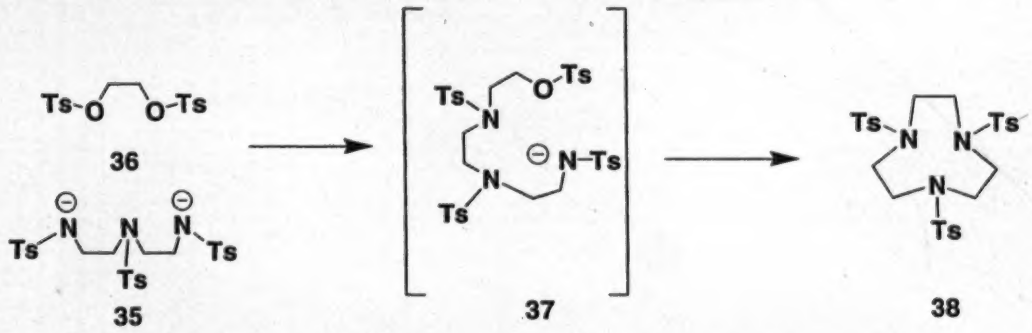
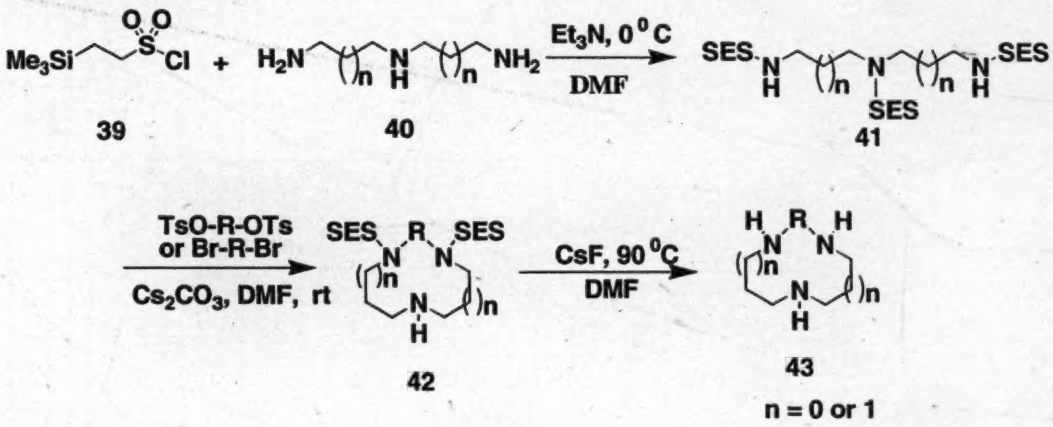


Figure 1. 13: Richman-Atkins protocol to triazacyclononane 38

A caveat with this methodology is that sulfonamides are fairly resistant to cleavage and therefore the detosylation must be carried out under fairly rigorous conditions such as concentrated sulfuric acid, or with hydrobromic and acetic acids, sodium or lithium in liquid ammonia, sodium naphthalenide or lithium aluminum hydride.

A modification of this Richman-Atkins procedure involves the use of Cs(I) to take advantage of the so called 'cesium effect'.[35] This term applies to two different synthetic phenomena. The first being the readiness by which cesium carboxylates dissolved in DMF can be alkylated with alkyl halides, and the second, and more relevant, is the beneficial effect that the use of cesium has on intramolecular cyclization versus an intermolecular reaction. It is believed that the cesium ion, relative to other alkali metal cations, directs the reaction in an intramolecular process suppressing the intermolecular reaction. Thus the method uses Cs_2CO_3 suspended in DMF with the appropriate bis-tosylamide and a dibromide or other leaving group. Again it was found that these cyclizations did not have to be performed under high dilution conditions.[36]

Recently Hoye, has attempted to overcome the problems associated with the use of the tosyl group.[37] The approach that the group undertook was to use β-trimethylsilylethanesulfonamides (SES-sulfonamides) for the preparation of macrocyclic polyamines (**41,** Scheme 1.7).

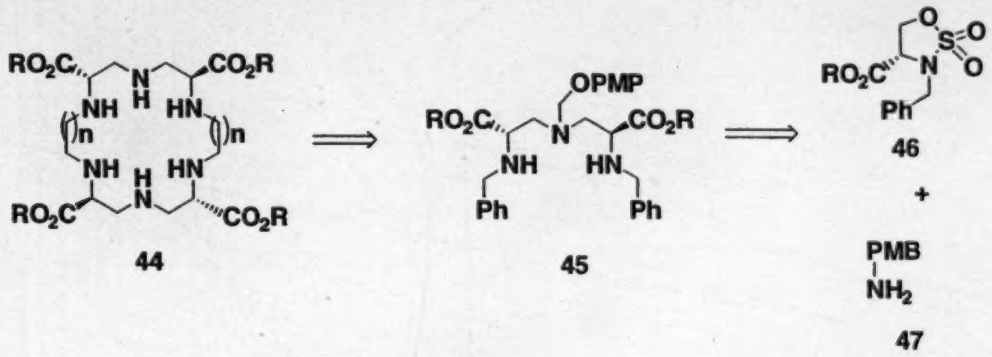


Scheme 1. 7

The authors have shown that the SES group can perform the same basic functions as the tosyl group, such as increasing the acidity of the remaining N-H group for deprotonation by relatively weak bases, preorganizing the favorable intramolecular cyclization relative to the intermolecular cyclization using the cesium cation, and protecting the remaining secondary nitrogen atoms that may be present in the structure. One major advantage behind using the SES group is that it can be cleaved under comparatively mild conditions, using CsF in DMF, as demonstrated in Scheme 1.7 by the transformation of **42** to **43**. This mildness, as pointed out by the authors, would offer a greater degree of compatibility for other functional groups in this reaction. A wide array of triazamacrocycles were prepared, including 1,4,7-triazacyclononane when R = CH_2, in 68% overall yield (Scheme 1.7) from the tri-SES protected triamine **41**. Moreover, the fluoride-induced decomposition of the SES-sulfonamide yields volatile products, simplifying purification of the final macrocycles.

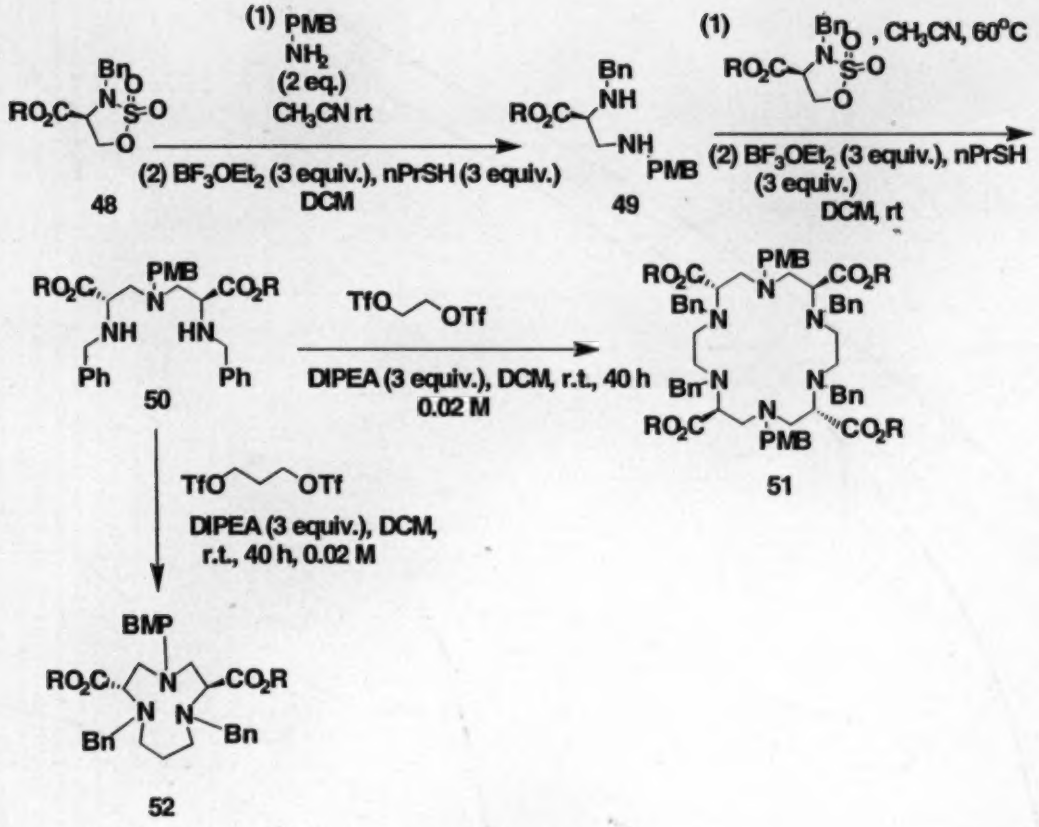
A potentially interesting approach to the synthesis of azamacrocycles has recently been described by Kim.[38] This method is one of only a few that attempts to position stereogenic centers close to the metal binding core on the carbon 'back-bone' of the ring.

This synthesis involves the ring opening of cyclic sulfamidates (**46**) as envisioned in the following retrosynthetic analysis (Scheme 1.8) to yield macrocyclic polyamines (**44**).



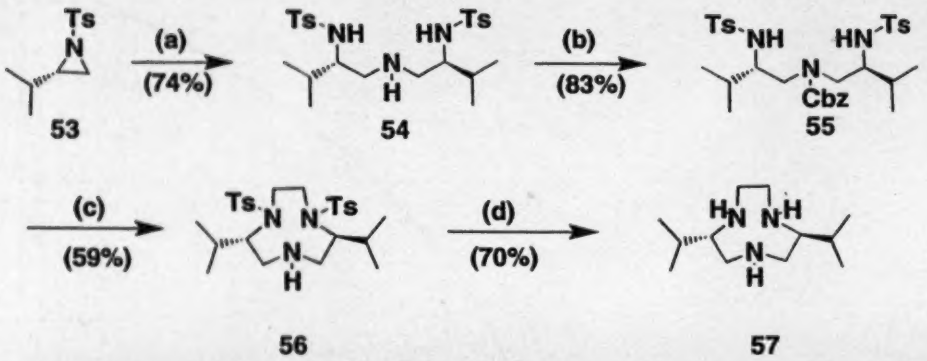
Scheme 1. 8

The opening of the cyclic sulfamidates **48** with *p*-methoxybenzylamine produced the acyclic precursors **49** necessary to construct the protected triamines **50**. The construction of the macrocycle was accomplished smoothly by treating the protected triamine **50** with the bistriflate of ethylene glycol to effect a double nucleophilic displacement (Scheme 1.9). The reaction was noted to proceed best with slow addition of the bis-triflate in the presence of *N,N*-diisopropylethylamine (DIPEA) under fairly dilute conditions. It was especially noted by the authors that the use of the bistriflate was essential for the success of this macrocyclization step and that the use of 1,2-dibromoethane, ethylene glycol bis(*p*-toluenesulfonate) or bismethanesulfonate were not successful. Of particular relevance to this project, it was shown that cyclization with ethylene glycol bistriflate produced the 18-membered macrocycle **51** and not the 9-membered macrocycle. However, cyclization using the 1,3-propanediol bistriflate proceeded smoothly, under the same conditions to afford the 'backbone' substituted azacyclodecane analogue **52** (Scheme 1.9).


(1) PMB NH2 (2 eq.) CH3CN rt
(2) BF3OEt2 (3 equiv.), nPrSH (3 equiv.) DCM
48
49
(1) , CH3CN, 60°C
(2) BF3OEt2 (3 equiv.), nPrSH (3 equiv.) DCM, rt
50
TfO OTf
DIPEA (3 equiv.), DCM, r.t., 40 h 0.02 M
51
TfO OTf
DIPEA (3 equiv.), DCM, r.t., 40 h, 0.02 M
52

Scheme 1. 9

The same laboratory has very recently published a route to the peraza-macrocycles using chiral aziridines.[39] The improvement over the previously reported method is that, for the first time, a synthesis of 'backbone' chiral 1,4,7-triazacyclononane ligands was possible. Thus, treatment of the chiral aziridine **53** (Scheme 1.10) with lithium azide, followed by reduction and aziridine opening, provided the bis-tosylated chiral triamine **54** in 74% overall yield. Protection of the free tertiary amine with a carboxybenzyloxy group gave **55,** which was followed by a Richman-Atkins cyclization using Cs_2CO_3 in DMF. This provided the protected 'backbone' chiral 1,4,7-triazacyclononane **56** in 59% yield under high dilution conditions.



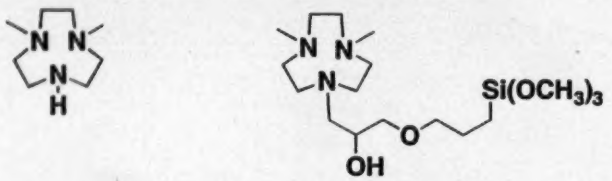
53 54 55 56 57

(a) (i) LiN_3, CH_3CN, (ii) H_2, Pd/C, MeOH, (iii) 53, CH_3CN; (b) CbzCl, TEA, CH_2Cl_2; (c) (i) 1,2-ethanediol bis(*p*-toluenesulfonate), DMF, Cs_2CO_3, (ii) H_2, Pd/C; (d) conc. H_2SO_4, heat

Scheme 1. 10

Again, it can be seen that a possible disadvantage is the removal of the tosyl groups under harsh acidic conditions (**56** to **57**). An X-ray crystal structure of the Ni(II) coordinated final product was obtained which showed the metal ion coordinated to two triazacyclononanes in an octahedral-like geometry.

Jacobs has described the preparation of a heterogenized tacn derivative 1,4-dimethyl-1,4,7-triazacyclononane (dmtacn **58** below).[40] The advantage of this ligand, as claimed by Jacobs, is that this ligand bears the methyl groups of tmtacn **13** (thereby suppressing its catalase activity) and also, the non-derivatized nitrogen atom in the ring can be used to attach a covalent tether, such as in **59** (Figure 1.14).



58 59

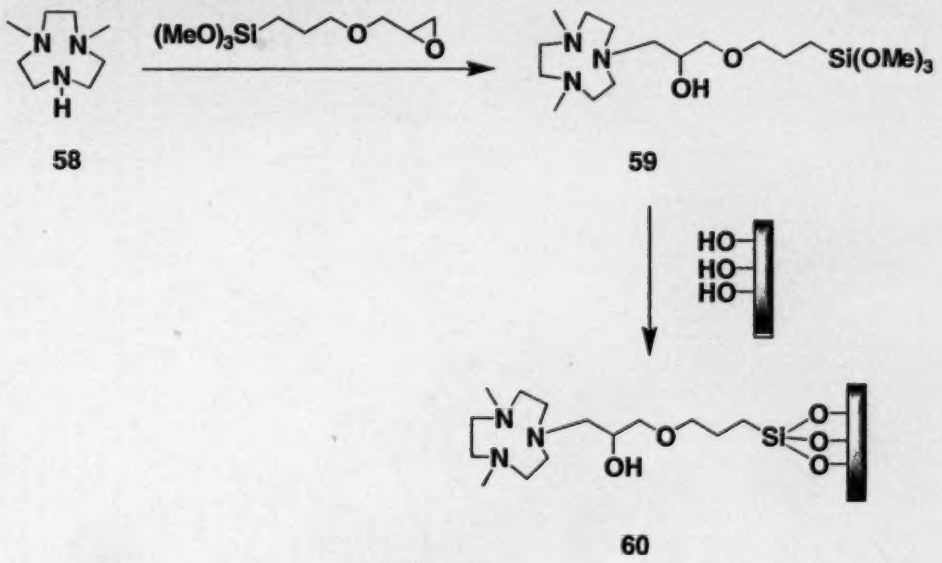
Figure 1. 14: dmtacn, 58, and its derivative, 59

The dimethylated compound was prepared via selective detosylation of tritosylated tacn, methylation of monotosylated tacn and detosylation in sulfuric acid. A comparison between the catalytic activity of this dimethylated dmtacn and that of the trimethylated version ensued, using styrene and 1-hexene in acetone as model substrates. The

epoxidation of styrene with Mn-dmtacn was comparable to that with Mn-tmtacn, however, the homogeneous Mn-dmtacn was inactive for the epoxidation of 1-hexene due to a large extent of peroxide decomposition.

Various approaches were attempted by this group to link the dmtacn ligand to a solid support, via its secondary nitrogen atom. This link was accomplished by a variety of methods utilizing silica as the solid support. One method used a 'reversed synthesis' by first treating dmtacn **58** with 3-(glycidyloxypropyl)trimethoxysilane to give **59** followed by immobilization on SiO_2, all yielded the heterogeneous catalyst **60** with loadings of about 0.2-0.8 mmol g^{-1} (Scheme 1.11).

The yields of epoxide product suggested that the best heterogeneous catalyst was prepared by the 'reversed' synthesis method. Most notably, whereas the homogeneous catalyst was inactive toward epoxidation of 1-hexene, the heterogenized catalyst gave satisfactory yields of 1,2-epoxyhexane.



58 **59** **60**

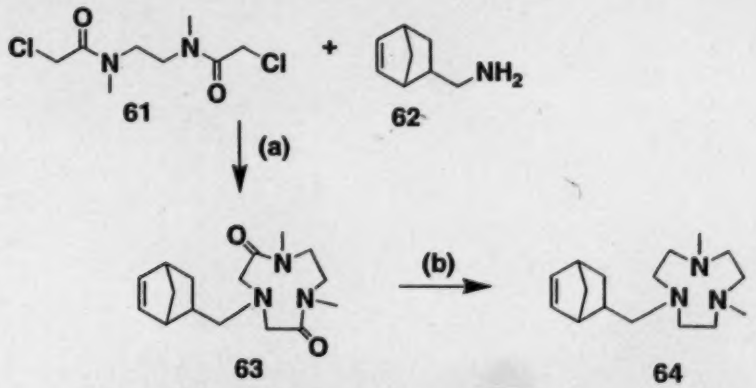
Scheme 1. 11

The catalytic activities reported for this system are much higher than those of the analogous systems, where the ligand has two additional 2-hydroxyalkyl pendant arms on the remaining nitrogen atoms, in place of two methyls.[41] However, although the conversions of the disubstituted olefins to epoxides are generally acceptable, these

reactions do suffer from a lower selectivity for the epoxide, with allylic oxidation and *cis*-diol formation being the predominant side reactions.

Hoping to improve upon the solid phase approach, an attempt was made to try to immobilize the tacn ligand, while keeping the desired properties of its 'free' triazacyclononane-manganese system. Thus, polymeric structures with a high density of 1,4,7-triazacyclononane side chains were prepared. The transformation was carried out utilizing a ring opening metathesis polymerization approach after formation of the monomer.[42]

The monomer **64** was constructed using a norbornene unit **62** through a bis(chloroacetamide) **61** cyclization-reduction sequence (Scheme 1.12). The final product **64** was purified using chromatograpy and isolated in 15% overall yield.



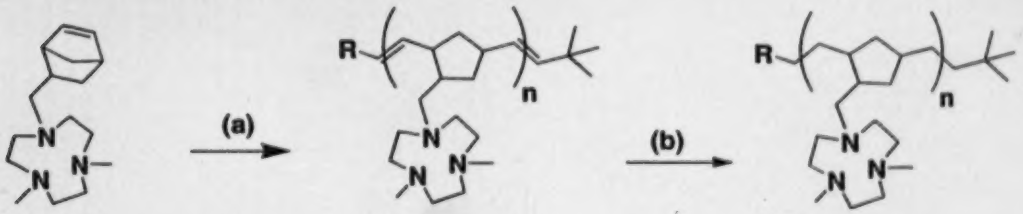
(a) Na_2CO_3, LiBr, CH_3CN, reflux, 12h (b) $LiAlH_4$, THF, reflux 6h

Scheme 1. 12

This substrate was now ready for polymerization. All attempts using Grubb's catalyst failed[43], however, by employing Schrock's molybdenum based catalyst[44] the desired polymer **66** was obtained in quantitative yield (Scheme 1.13). The polymer terminal ends were capped with pivalaldehyde after the monomer building blocks were consumed. The polymer was also saturated through diimide-mediated hydrogenation.

Preliminary studies with the catalyst, using 1 mol% of active catalyst, were carried out and showed that the polymeric azamacrocycle had comparable activity to that of its corresponding monomeric azamacrocycle through the efficient conversion of

simple aromatic olefins to the corresponding epoxides. However, in a few of the reported cases, most notably α-methylstyrene, there was a considerable amount of diol formation. This system was also capable of epoxidizing aliphatic alkenes. Internal *Z*-alkenes were more effectively converted to their epoxides than terminal or *E*-olefins. Hydroxyl groups in the allylic or benzylic positions were also oxidized whereas α,β-unsaturated carbonyl compounds were fairly unreactive.

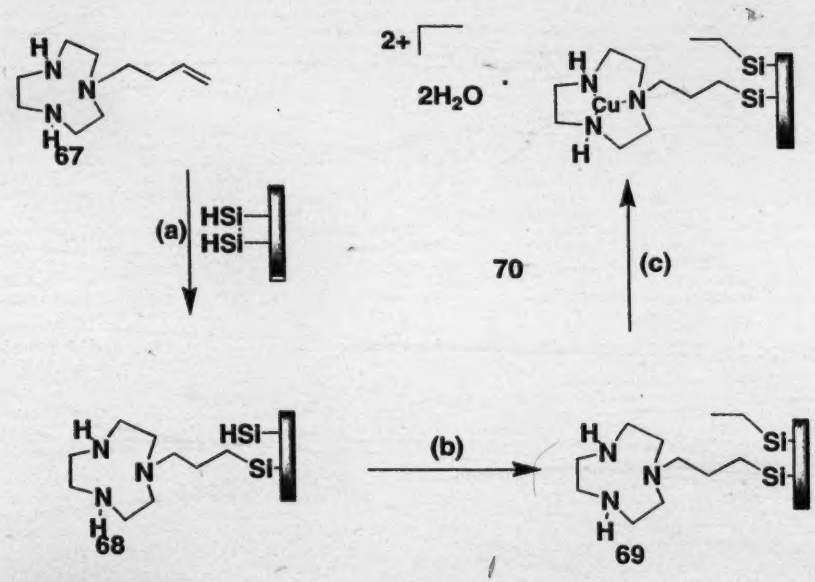


64 65 66

(a) (i) Schrock's catalyst (5 mol%), toluene, rt, 4 h (ii) pivalaldehyde (b) *p*-tolylsulfonylhydrazide, NaOH, bis(ethylene glycol) methyl ester 120 °C-130 °C, 1.5 h

Scheme 1. 13

Burstyn has reported another method of linking these reagents onto a solid support. This report described the synthesis of a copper (II) triazacyclononane linked to a silica support for applications in the heterogeneous hydrolysis of a phosphodiester.[45]



(a) $RhCl(PPh_3)_3$, toluene, reflux, 3 days (b) C_2H_4, $RhCl(PPh_3)_3$, toluene, 25 °C, 15 h; (c) $Cu(NO_3)_2$ (aq)

Scheme 1. 14

The supported catalyst **70** (Scheme 1.14) was prepared through a rhodium catalyzed hydrosilation reaction between *N*-(4-but-1-enyl)-1,4,7-triazacyclononane **67**, and hydride-modified silica. The *N*-(4-but-1-enyl)-1,4,7-triazacyclononane and the silica were refluxed together in toluene for three days in the presence of Wilkinson's catalyst, covalently linking the macrocycle to the support (**68**). Reacting the silica with ethylene then blocked the unreacted hydrides on the surface of the silica (**69**). This catalyst was shown to be effective over a period of many months for the heterogeneous hydrolysis of a phosphodiester.

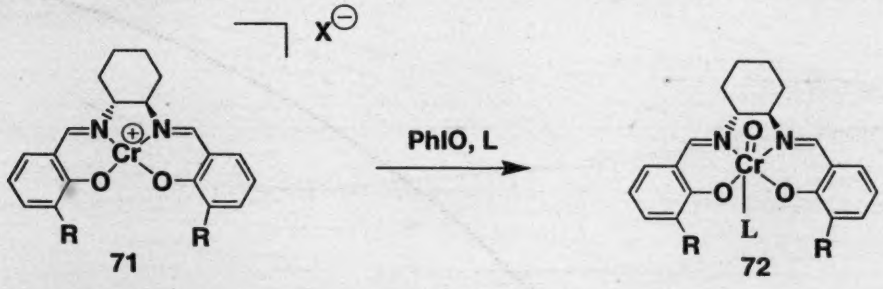
1.3.3: Synthesis of Tacd (13) and Derivatives

Besides the synthetic methods based on Richman-Atkins cyclization techniques previously mentioned, and through the ring opening reactions of cyclic sulfamidates, the synthesis and properties of the tacd compounds remain largely unexplored. In a manner analogous to the tacn (**12**) derivatives, the synthesis of these compounds has been achieved mainly through the modification of the secondary nitrogen atoms of the heterocycle.

1.4: Perspective and Objective of the Project

Interest in the development of efficient chiral catalysts, for use in the epoxidation of olefins, in particular with enantio-control, remains high. Systems to particularly note are those developed by Sharpless, Jacobsen/Katsuki, and Shi.[46]

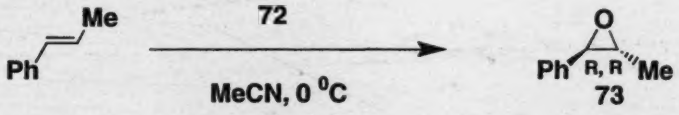
However, there are problems associated with these systems. In most cases there is a better selectivity for the epoxidation of (*Z*)-alkenes (as for the Jacobsen manganese salen complexes) than that for the (*E*)-alkene. Recently, Gilheany published interesting results based on a chromium salen complex (**71**, Scheme 15). In this case the selectivity of epoxidation with active catalyst **72** is better with the (*Z*)-alkenes than with the (*E*)-alkenes and an e.e. of up to 92% has been achieved with the model compound (*E*)-β-methylstyrene.[46]



R = CF_3, Cl, F, Ph, H

X = NO_3, PF_6

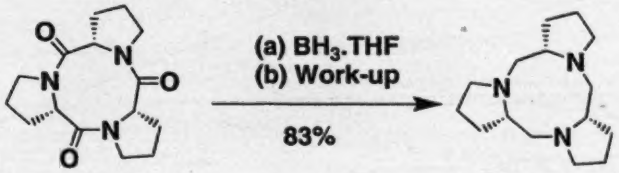
L =Ph_3PO, pyridine *N*-oxide, DMF, DMSO



Scheme 1. 15

The development of other types of chiral epoxidation catalysts is certainly beneficial and it appears that those based on a triazacyclononane structure **12** are worth exploring. The use of amino acids as building blocks for the triazacyclononanes would be advantageous by potentially providing for a great deal of structural diversity. Surprisingly, besides the recent report by Kim[39], there has been very few reports on the development of routes to these catalysts starting with amino acid precursors.

One report, however, did take advantage of a cyclic derivative of a triproline peptide, cyclo(tri-L-prolyl) **74** (Scheme 16).[47] Exhaustive reduction of the cyclic skeleton with borane-tetrahydrofuran followed by an acidic workup and extraction with base gave the cyclic triamine **75** in 83% yield. Further studies of the Mn-complexed ligand compared with the 1,4,7-trimethyl-1,4,7-triazacyclononane showed that their redox behaviour is similar, however, the alkene epoxidation properties were not investigated.



74 **75**

Scheme 1. 16

This focus of the work outlined in this thesis is on the development of a general method for the synthesis of chiral macrocyclic polyamines on a solid-support scaffold. It utilizes chiral α-amino acids as building blocks, providing an access to a variety of derivatives of tacn **12**, containing stereogenic substituents on the carbon 'backbone' (Figure 1.15). This project utilizes techniques developed in our laboratory for the solid-supported synthesis of linear polyamines via the exhaustive reduction of peptides and mild oxidative cleavage of the resultant borane-amine adducts, as well as a novel cyclization protocol for the formation of the desired chiral triazamacrocycle.

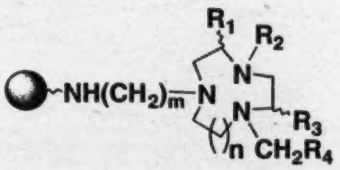


Figure 1. 15: general structure of chiral macrocyclic polyamines

2. Solid-Phase Synthesis of Resin-Bound Oligoamines

2.1: Linker Synthesis

The preparation of the polyamines began by expanding upon the work developed by Manku and Laplante in our laboratories.[12] The resin that was chosen for the solid-phase synthesis was tritylchloride beaded polystyrene cross-linked with 1% divinylbenzene (Figure 2.1). This resin was selected for a variety of reasons. Firstly, the site of linker attachment would be rendered unreactive due to the presence of the bulky trityl group. Secondly, the swelling properties of this resin in a variety of solvents would allow us to exploit its reactivity by allowing access to the majority of the reactive sites found on the bead's interior. Thirdly, this resin is stable under basic conditions and the products can be released from the solid support through cleavage of the linker under acidic conditions (in general 5% trifluoroacetic acid, TFA, in dichloromethane).

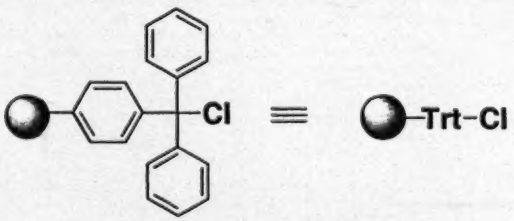
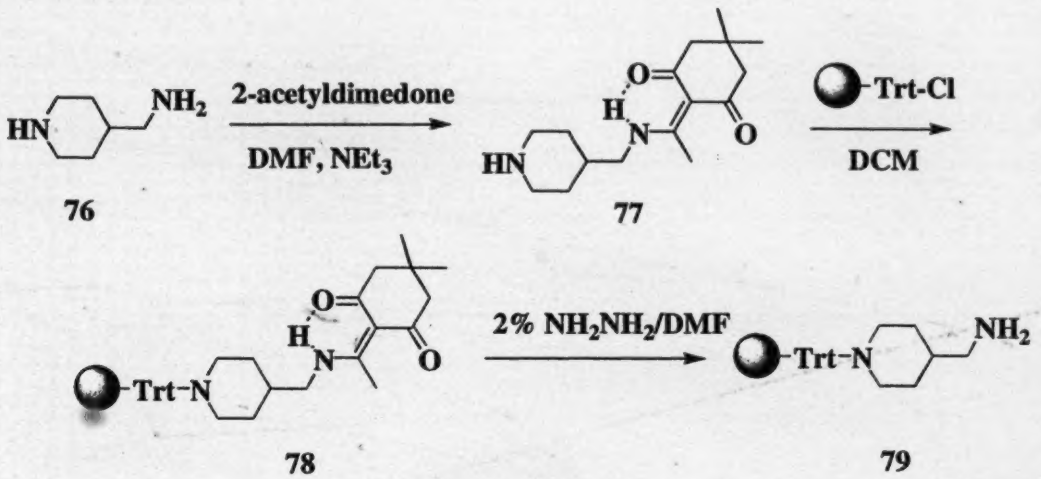


Figure 2. 1: tritylchloride polystyrene (PS-Trt-Cl)

Initially, 1,3-diaminopropane was used as the spacer because of the work done previously in our laboratories. A new, more rigid, linker based on 4-aminomethylpiperidine **76** (see below) was also constructed.

1,3-diaminopropane is very soluble in CH_2Cl_2, a solvent that is ideal for the swelling of the polystyrene matrix. Elucidation of the conditions for the reduction of the resin-bound oligopeptides and some model studies were performed using this linker. However, it was imagined that this short 1,3-diaminopropane linker length could be problematic for the envisaged cyclization reactions. Subsequently, longer linkers such as 1,8-diaminooctane and 1,12-diaminododecane were developed in order to prevent reaction at the amine anchor of the spacer.

The preparation of the 4-aminomethylpiperidine linker **79** was not as straight forward as that of the symmetrical diamines. Its synthesis is outlined in Scheme 2.1 below.



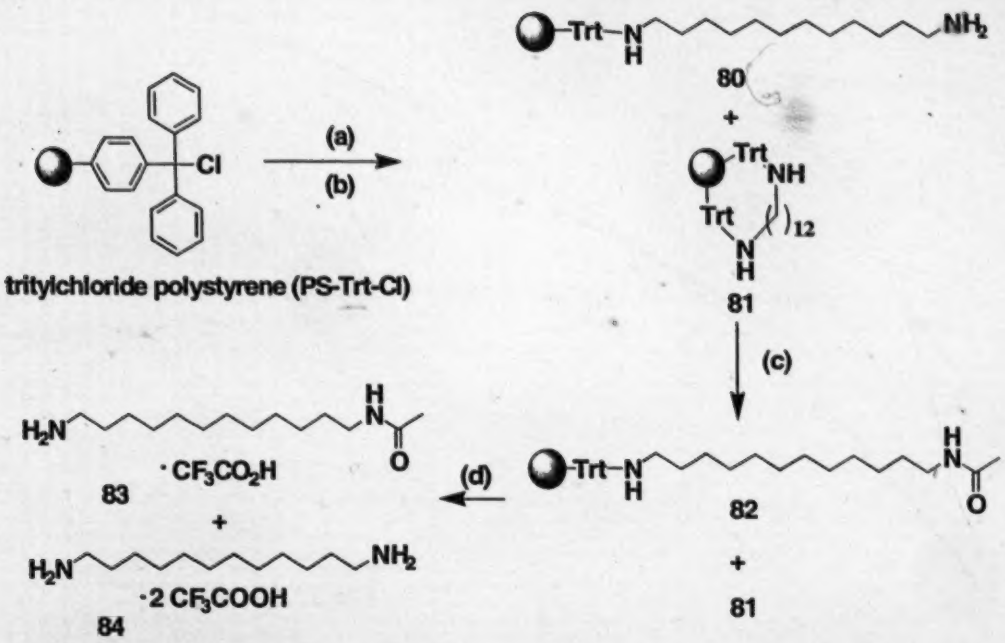
Scheme 2. 1

The synthesis began with the selective protection of the primary amine over the secondary amine by using 2-acetyldimedone.[48-50] This reagent's selectivity comes from its ability to form stabilizing hydrogen bonds with the remaining hydrogen of the primary amine. Selective protection of the primary amine gave protected diamine **77** and allowed the attachment of this diamine to the support selectively through its secondary amine to give **78**. Subsequent cleavage of the protecting group using hydrazine liberated the resin bound primary amine **79**, as visualized by a ninhydrin colorimetric assay.[51]

The preparation of the longer diamine spacers presented other challenges. Typically, a solution of 1,12-diaminododecane (50 equiv.) in CH_2Cl_2 was treated with tritylchloride-PS in small portions over a period of one hour (to ensure maximum diamine concentration relative to the reactive sites) and the resin was stirred at room temperature for 3 hours at which point it was rinsed and washed and then vortexed with a mixture of CH_2Cl_2/MeOH for 2 more hours to ensure that any unreacted sites had been capped as an ether. This diamine was chosen because of its length to minimize possible chances of reaction at the resin bound tritylamine in the envisioned cyclization reactions for the ultimate target of this project. It was predicted that the steric environment

provided by the three aromatic rings would inhibit its reactivity. A large excess of this diamine was used in order to reduce the chances of both primary amine ends reacting at different resin sites to form cross-linking. However, because the solubility properties of this diamine in dichloromethane were poor, the proportion of diamine in solution was far less than the desired 50 equivalents. Subsequent reaction of a small portion of resin **80** with acetic anhydride in triethylamine transformed the free primary amine to amide **82**. This protection step was necessary in order to determine the percentage of the bound diamine that was cross-linked (compound **81**). The degree of cross-linking of a solid support is related to the ability of the resin to swell in solvents. In order to perform reactions on solid support, the resin must be adequately swelled to allow solute to access the reactive sites.[52,53] The cross-linked species was not expected to react with acetic anhydride. After the reaction, a sample of resin **82** containing the cross-linked species was cleaved with 5% TFA/DCM for analysis and it was discovered that there was substantial cross-linking (Scheme 2.2) as evidenced by the electrospray mass spectrum and UV trace that contained a substantial amount of diamine **84** (post cleavage).

To reduce the percentage of diamine cross-linking it was necessary to explore other solvent systems that would be compatible both with the swelling properties of the resin and the solubility characteristics of the diamine. For this purpose *N,N*-dimethylformamide (DMF) was selected. Although the solubility of the diamine was relatively poor at room temperature, it was found that the solubility could be increased by increasing the temperature. Thus optimal solvent conditions for this reaction were found to be at 80 °C in DMF. These conditions allowed for the effective concentration of the diamine in solution to increase, and therefore this reduced the proportion of cross-linking. Treatment of a portion of this resin with acetic anhydride and Et_3N in DMF and subsequent cleavage of the resin with 5% TFA/DCM provided the mono-acetylated diamine **83** as its TFA salt. The latter was observed by LC-MS-UV, and analysis of the data showed that the resin was 90% free of the cross-linked species.



(a) 1,12-diaminododecane; DCM, RT, 12 h; (b) MeOH, RT, 2 h (c) Ac_2O, NEt_3, DMF (d) 5% TFA/ DCM

Scheme 2. 2

It was then possible to synthesize the desired oligoamines from their corresponding oligoamide precursors on solid support by using standard peptide synthesis methods with Fmoc-amino acids.

It was expected that the use of a more soluble linear diamine linker would eliminate the problem of cross-linking and thus provide access to purer starting resin. The use of 1,8-diaminooctane was investigated. It was found that this diamine was relatively insoluble in CH_2Cl_2, which increased the proportion of cross-linking product **85** (Figure 2.2). The diamine was found to be more soluble in DMF. Thus heating the diamine in DMF at 50 °C gave resin **86**, followed by rinsing, and treatment of a small portion of the resin with Ac_2O/Et_3N in DMF, provided the acetylated amine **88** on solid support. Cleavage of this small portion of resin thus afforded crude product **89** that was analyzed by LC-MS-UV. The analysis showed that the resin was >98% free of diamine **87** with acetylated amine **89** as the only visible peak by HPLC. This resin was then used in standard peptide synthesis using Fmoc-amino acid building blocks.

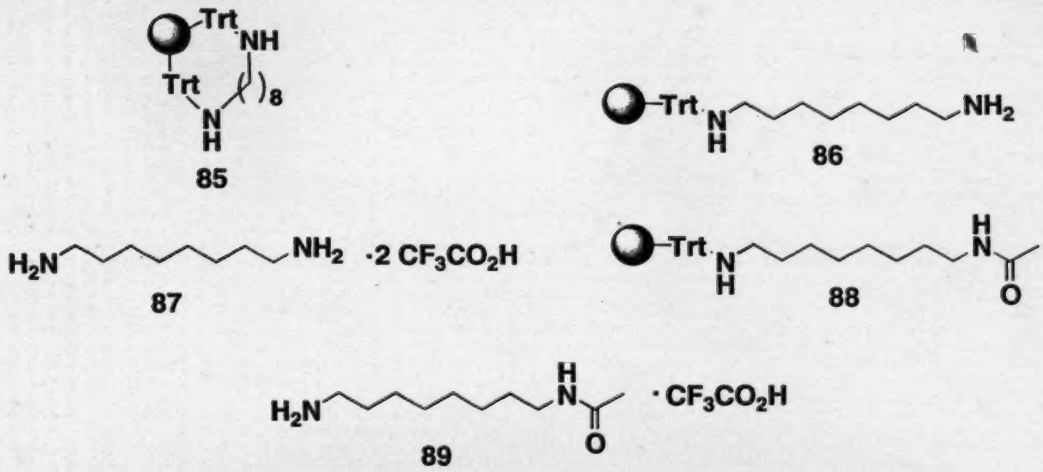
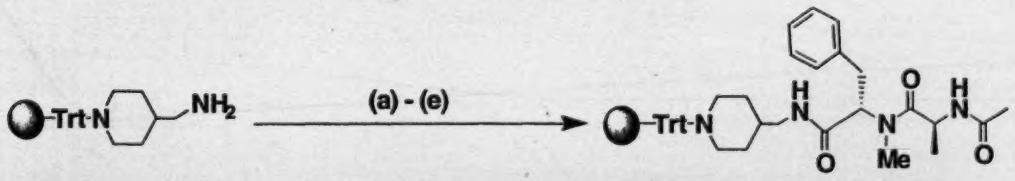


Figure 2. 2: 1,8-diaminooctane linker 86 and cross-linked species 85

2.2: Synthesis of Resin-bound Polypeptides and Polyamines

The 4-aminomethylpiperidine tritylpolystyrene **79** was easily elaborated using standard peptide synthesis with Fmoc-amino acids (Scheme 2.3).



79 90

Reaction conditions: (a) 4 equiv. Fmoc-L-N-Me-Phe-OH, 4 equiv. HOBt, 4 equiv. HBTU, 8 equiv. DIPEA, DMF, r.t., 3 h (b) 20% piperidine/DMF 45 min. (c) Fmoc-L-Ala-OH, 4 equiv. HATU, 8 equiv. DIPEA, DMF (d) 20 % piperidine/DMF (e) Ac_2O, NEt_3, DMF.

Scheme 2. 3

The use of *N*-methylated amino acids would be necessary in the synthesis so that upon the reduction of the desired tripeptide a central tertiary amine residue would result. The latter should be slower to react in the subsequent macrocyclization protocol to form the desired medium-ring triazacycloalkane. Thus, commercially available *N*-methylated Fmoc-amino acids, such as Fmoc-L-N-Me-Phe-OH, were purchased. The coupling agents that were used for the attachment of the first amino acid residue to the diamine-conjugated polystyrene resin were HOBt[54] and HBTU[55] (Figure 2.3). The

coupling reactions proceeded without epimerization (as seen by LC-MS). Cleavage of the Fmoc protecting group with 20% piperidine in DMF afforded an *N*-methylated secondary amine that was further extended using the coupling reagent HATU (Figure 2.3) and Fmoc-L-Ala-OH. This type of coupling, to form tertiary amides on solid-phase, is known to be a particular challenge. The HATU reagent, developed in 1993 by Carpino[56], was found to give better yields over other amino acid coupling reagents such as BOP, PyBrop, and HBTU for the coupling of sterically hindered or *N*-methylated amino acids.[57,58] Cleavage of the Fmoc protecting group with 20% piperidine/DMF and capping of the peptide with an acetate group gave the desired tripeptide **90** (above) in good yield and purity (LC-MS).

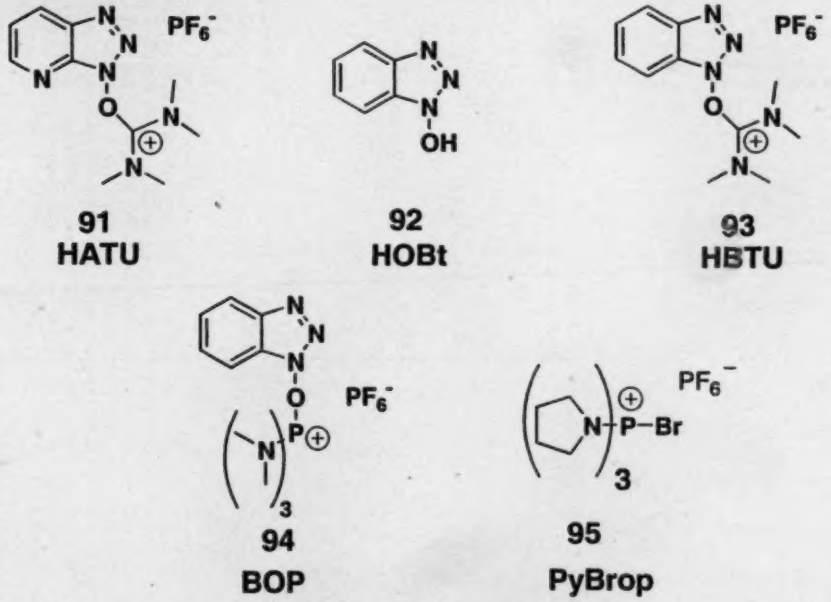
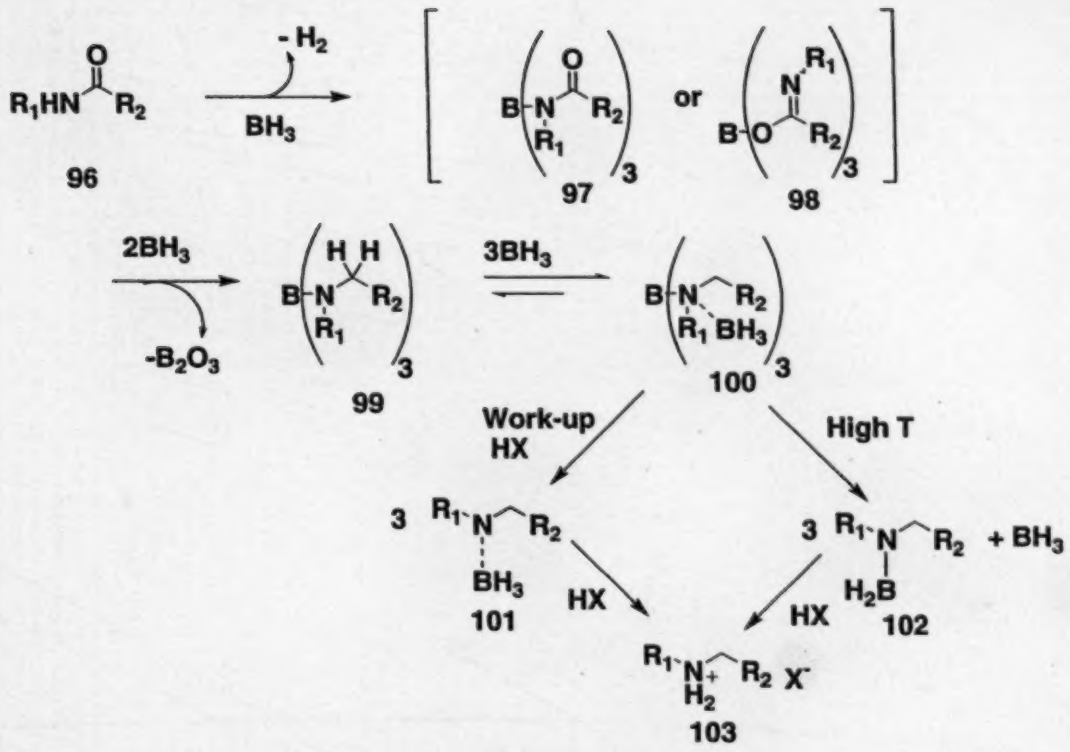


Figure 2. 3: coupling reagents

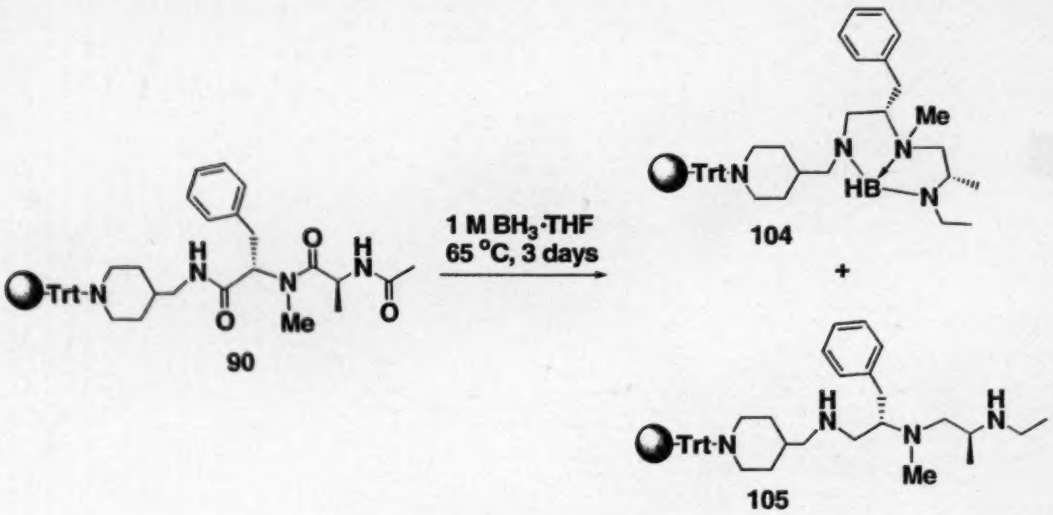
The reduction of the resulting peptide was performed by using the protocol developed in our laboratories.[12] This procedure involved the treatment of the resin-bound peptide with a large excess of a 1 M borane-tetrahydrofuran complex, followed by oxidative workup with I_2 in an acetic acid/acetate buffer of approximately pH 4-5. The mechanism of the reduction of secondary amides with borane is presumed to proceed as shown below (Scheme 2.4).



Scheme 2. 4

The first equivalent of borane is thought to react with the amidic hydrogens of **96** with the concomitant release of hydrogen gas. The resulting intermediate **97** or **98** would then require an additional 2 equivalents of hydride per amide to fully reduce it to the second intermediate, **99**. Intermediate **99** is known to form stable adducts with the borane and is not as effective at the reduction of the initial borane-amide complex under normal condtions. Thus at lower temperatures excess borane is employed in the protocol to ensure the complete reduction of all the amide units. The buffered oxidative workup to cleave borane-amine adduct **101** was found to be mild enough not to affect the cleavage of the substrate from the resin.

Thus, the reduction of this tripeptide **90** (Scheme 2.5) and subsequent oxidative cleavage of the borane-amine adducts, analogous to **101** above, was carried out and yielded some interesting results.



Scheme 2. 5

The reduction of **90** initially gave mixtures of mono-reduced, di-reduced, and completely reduced products. It became necessary to increase the reduction times from 24 h to 72 h in the hope that longer reaction times would increase the proportion of fully reduced triamine **105**, as has been previously demonstrated for the reduction of sterically hindered oligoamides in our laboratory.[12] This process was followed by the usual oxidative workup. Interestingly, after cleavage of the substrates from the solid support using 5% trifluoroacetic acid in CH_2Cl_2, a significant $[M+11]^+$ peak was observed in the electrospray mass spectrum, along with the molecular ion corresponding to the linear triamine derived from **105**. The isotope pattern for this peak indicated that it contained a boron atom, which was subsequently confirmed by HRMS, and ^{11}B NMR spectroscopic analysis revealed a single peak with a chemical shift of 19.49 ppm consistent with a tetracoordinated species. Thus, structure **104** (Scheme 2.5) was proposed which seemed to fit the experimental data. Due to these results, a modification of the workup was necessary in order to extrude boron from **104** and provide **105**.

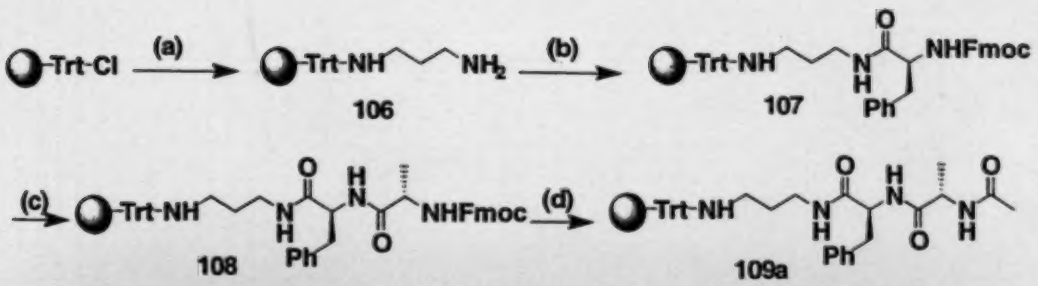
It then became necessary to explore various conditions which would favour cleavage of the resilient aminoborane adduct and liberate the resin-bound triamine **105**. The table below summarizes these experiments. The experimental conditions were run for 24 hours.

Table 2.1: Reduction protocol modification

Resin (g)	DIPEA (2 ml/g resin)	AcOH (4 ml/g resin)	Ethylene Glycol (ml)	I_2	THF (ml)	Result
(1) 0.050	----------	0.200 ml	0.100 ml	15 equiv.	0.600 ml	No change
(2) 0.050	0.100 ml	----------	0.200 ml	------	0.700 ml	Largest increase in proportion of **105**
(3) 0.050	0.100 ml	----------	0.200 ml	15 equiv.	0.700 ml	Small increase in proportion of **105**
(4) 0.050	0.100 ml	----------	0.100 ml	------	0.800 ml	Large increase in proportion of **105**

The conditions that were selected corresponded to entry 2 in Table 2.1 since it provided the best result (by mass spectrometry and ^{1}H NMR spectroscopy) showing the disappearance of aminoborane adduct **104** and only triamine **105** after substrate cleavage from the resin. As a result it became possible to cleanly synthesize polyamines containing both secondary and tertiary amines in good yield. We now could begin work on the 1,3-diaminopropyl polystyrene resin introduced by our group[12] in order to develop a general method of accessing polyalkylated polyamines.

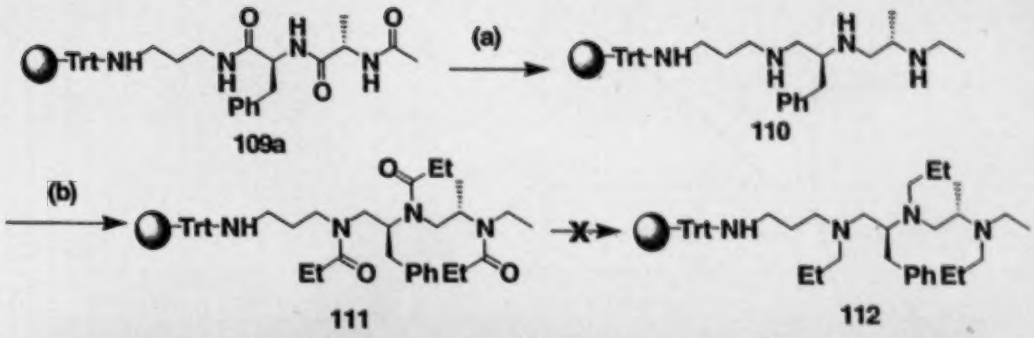
The design and synthesis of the peptides used for the studies was based on the work of Manku and Laplante in our laboratories[12] as well as the work just described with the 4-aminomethylpiperidine. Attachment of the diamine linker to the solid support was accomplished by the slow addition of the chlorotrityl polystyrene to a solution of a large excess of the diamine (typically 50-100 equivalents). For the studies, a peptide consisting of L-Phe and L-Ala residues (**109a**) was constructed (Scheme 2.6).



(a) (i) 1,3-diaminopropane (100 equiv.), DCM (ii) MeOH (b) Fmoc-L-Phe-OH (4 equiv.), HOBt (4 equiv.), HBTU (4 equiv.), DIPEA (8 equiv.), DMF (c) (i) 20% piperidine/DMF (ii) Fmoc-L-Ala-OH (4 equiv.), HOBt (4 equiv.), HBTU (4 equiv.), DIPEA (8 equiv.), DMF (d) (i) 20% piperidine/DMF (ii) Ac_2O, NEt_3, DMF, 2 h.

Scheme 2. 6

The first objective of this project was to synthesize oligo(*tert*-amines), which are relatively difficult to access using standard solution-phase chemistry for the reasons mentioned earlier, such as the use of extensive protection and deprotection schemes, and the necessary purification of complex mixtures. Standard amide coupling reactions rates between terminal secondary amines and activated amino acids tend to be rather sluggish, and so a route to oligo(*tert*-amines) was devised based on oligo(*sec*-amines) as precursors. Initially it was hoped that direct acylation of the oligo(*sec*-amines) and their subsequent exhaustive reduction would provide the desired oligo(*tert*-amines). Thus, reduction of the tripeptide **109a** (Scheme 2.7) with 1 M borane-THF and subsequent cleavage of the borane-amine intermediate via our buffered iodine-promoted work-up provided the desired oligo(*sec*-amine) **110**. This amine was then acylated with propionyl chloride to provide the desired oligo(*tert*-amide) **111** in good yield.



Reaction conditions: (a) (i) BH_3·THF, 65 °C, 24 h (ii) I_2 (20 equiv.), DIPEA (2 ml/g resin), AcOH (4 ml/g resin), THF (b) propionyl chloride, DIPEA, THF (c) (i) BH_3·THF 65 °C, 24 h (ii) I_2 (40 equiv.), DIPEA (2 ml/g resin), AcOH (4 ml/g resin), THF.

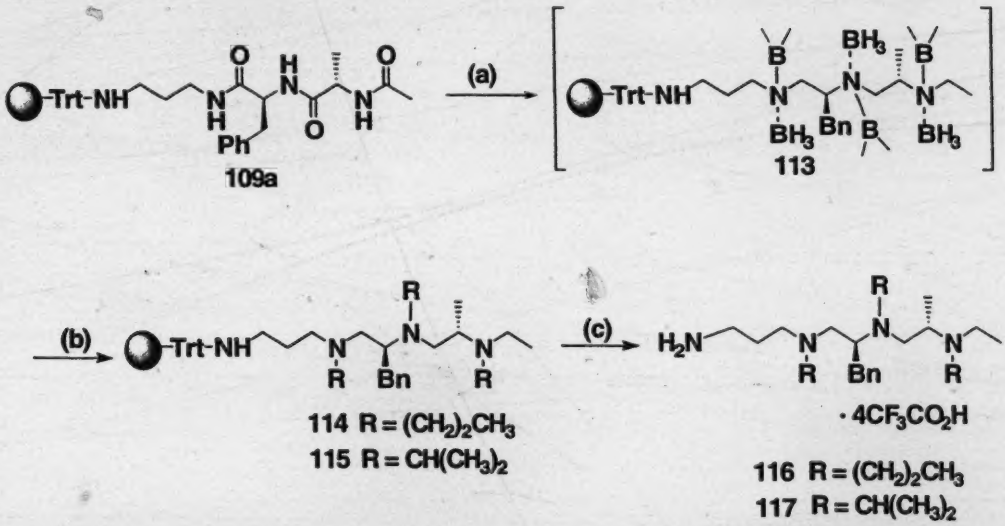
Scheme 2. 7

The reduction of oligo(*tert*-amide) **111** with 1 M borane-tetrahydrofuran solution followed by our buffered oxidative workup proved to be extremely difficult. The result of this protocol was a complex mixture of partial reduction products, with little of the desired tertiary amine **112** (Scheme 2.7), even after 5 days at 65 °C.

This experiment was also repeated with benzoyl chloride, in an attempt to obtain the polybenzoylated analogue, with similar results.

It has previously been reported in the literature that borane-amine adducts can serve as hydride donors for the reductive amination of aldehydes.[59-61] Thus, we attempted to synthesize directly the oligo(*tert*-amines) from the oligo(borane-amine) intermediate by reacting the aldehyde component with intermediate **113** shown below (Scheme 2.8) without subjecting the resin to our oxidative work-up conditions. Initially, the resin was treated with the aldehyde component and stirred for 48 h. Subsequent cleavage with 5% TFA/ DCM of a small sample of the resin showed that there was some fully alkylated product, as desired, but that the predominant products showed incomplete alkylation. This problem was eventually surmounted by the *in situ* addition of sodium triacetoxyborohydride as an external hydride source, based on precedent in the literature.[62] Thus the desired oligo(*tert*-amines), shown in Scheme 2.8, were obtained in good yield and good purity as seen by LC-UV-MS (>85% yield, >80% pure). Notably,

the use of a branched aldehyde, isobutyraldehyde, also proceeded smoothly to give the desired compounds **115** and **117**.



Reaction conditions: (i) 1 M BH_3·THF, 65 °C (ii) THF rinses (b) add RCHO, $NaBH(OAc)_3$, DMF, 48 h (d) 5% TFA/DCM.

Scheme 2. 8

When this procedure was used with benzaldehyde the formation of putative bridged *N,N*-acetals was observed and their structures, based on elecrospray mass spectroscopic data, have been tentatively assigned as **118** and **119** and **120** (Figure 2.4). Variations of the above procedure, such as the use of 10% acetic acid as co-solvent, gave the same results. It is apparent that this intramolecular side-reaction competes with the hydride addition to the iminium intermediate in the case of aromatic aldehydes.

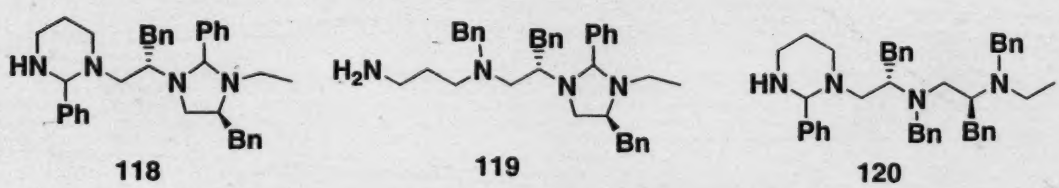
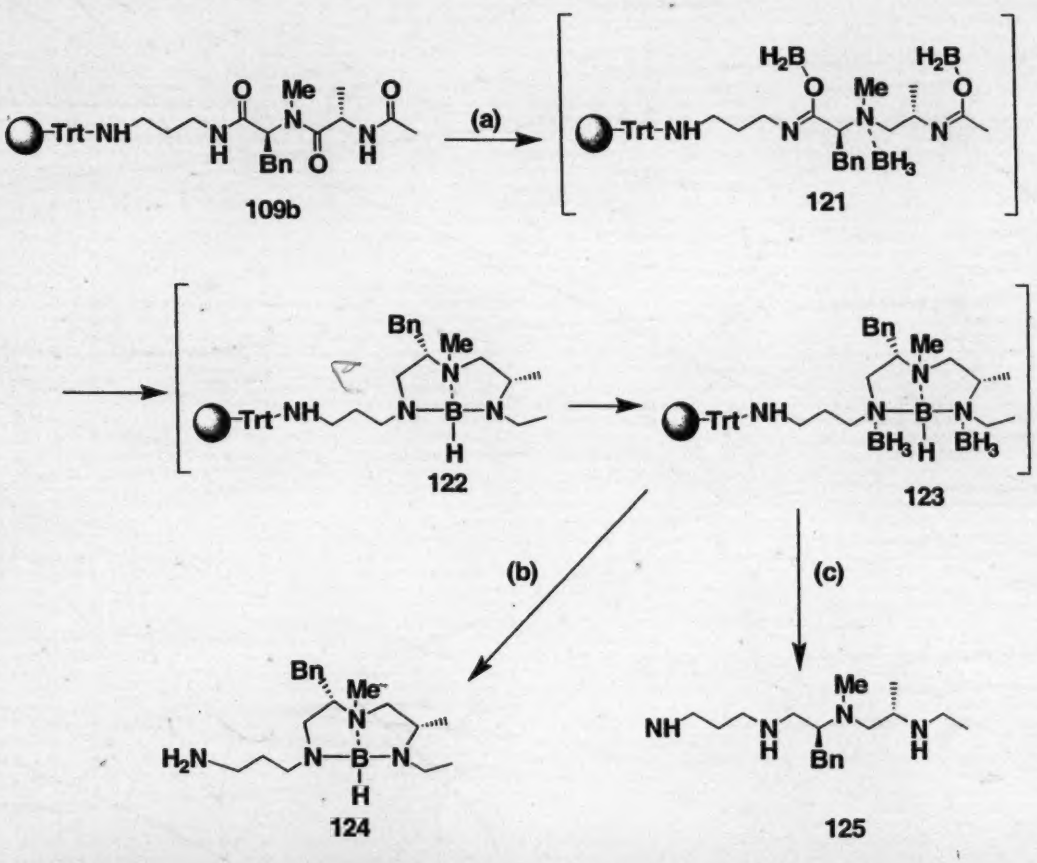


Figure 2. 4: structures of putative *N,N*-acetals

Most interestingly, however, was the result obtained upon reduction of the model peptide **109b** (Scheme 2.9) containing a central *N*-methylated phenylalanine residue. The usual iodine promoted workup and subsequent cleavage of a small sample of the resin (path (c) in Scheme 2.9) led to the isolation of a triaminoborane adduct **124** as the major product, which was analogous to what was observed with the 4-aminomethylpiperidine linker containing an internal tertiary amide (see Scheme 2.5). The presence of this compound was confirmed by ^{11}B NMR, which showed a peak at of δ 18.3 ppm that is consistent with a tetracoordinated species. The boron extrusion protocol with ethylene glycol that had been previously developed was used in order to remove the boron. Tentatively, our explanation for this phenomenon is attributed to the faster rate of reduction of tertiary amides with diborane.[63] Thus the initially formed aminoborane adduct **121** allows a rather facile intramolecular hydride delivery to occur to give intermediate **122** (which may also pick up additional equivalents of borane to form **123**). After the respective workup protocols either the triaminoborane or the desired polyamine would be generated and, after release from the solid support, give **124** and **125** respectively.[63]



Reaction conditions: (a) 1 M BH_3-THF, 65°C, 24 h (b) (i) I_2, 1:2:7 DIPEA/AcOH/THF, rt, 4 h (ii) Et_3N/DMF rinses (iii) 5% TFA/DCM (c) (i) I_2 1:2:7 DIPEA/AcOH/THF, rt, 4 h (ii) $HO(CH_2)_2OH$, DIPEA, THF, 24 h (iii) 5% TFA/DCM.

Scheme 2. 9

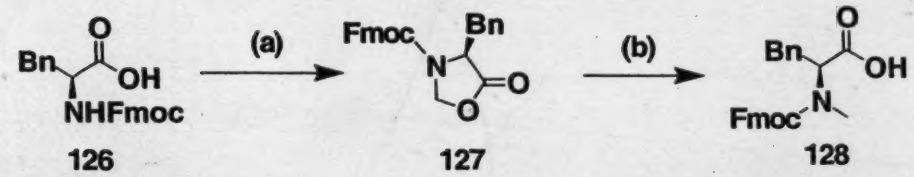
2.3: Design And Synthesis Of Solid-Support Immobilized Oligoamines As Precursors For The Chiral Derivatives Of 1,4,7-tacn (12) and 1,4,7-tacd (13)

The design of the polyamine precursors followed an approach largely based on the methodology that had been developed in the synthesis of the 4-aminomethylpiperidine and 1,3-diaminopropyl polystyrene linked oligoamines.[12] The goal of the project was to develop a general route to synthesize triazacycloalkane macrocycles that mimicked both the structure and reactivity of the tacn (**12**) and tmtacn (**13**) systems. To achieve this goal a series of polyamines was required in order to (a) synthesize a series of triazacycloalkanes and (b) determine the functional group

generality for the ensuing macrocyclization reaction. The advantage of our methodology is that it provides an expedient method for accessing polyamine cores that contain stereogenic centers because of the use of chiral amino acids as building blocks. For the purposes of this project it was necessary to obtain *N*-methylated amino acids as the first amide residue so that on subsequent cyclization of the resulting oligoamine, the central tertiary nitrogen would be less reactive than the secondary amines on either side. In general quaternization reactions proceed more slowly. All *N*-methylated amino acids were either synthesized according to the literature protocol described below, or purchased from commercially available sources.

2.3.1: Synthesis Of *N*-Methylated Amino Acids[64]

The synthesis to obtain the *N*-methylated amino acids was based on cyclization followed by reduction (Scheme 2.10). Starting from an enantiopure, commercially available, Fmoc-protected α-amino acid, such as Fmoc-L-Phe-OH **126**, and treating it with paraformaldehyde with catalytic *p*-toluene sulfonic acid in toluene at 100 °C, led to the formation of the desired compound **127** in good yield. The formation of this intermediate was confirmed by ES-MS. The subsequent ring opening reaction was carried out in chloroform with triethylsilane in the presence of trifluoroacetic acid. This reaction gave the desired Fmoc-protected- *N*-methylated-α-amino acid **128** in good yield. Its formation was confirmed by ES-MS. Compound **128** was used immediatedly in the standard peptide coupling reaction described earlier. This was the only synthesis of an *N*-methylated amino acid and was intended to show that the starting materials for our synthesis are readily accessible by standard solution-phase chemistry. All subsequent *N*-methylated amino acids were purchased.

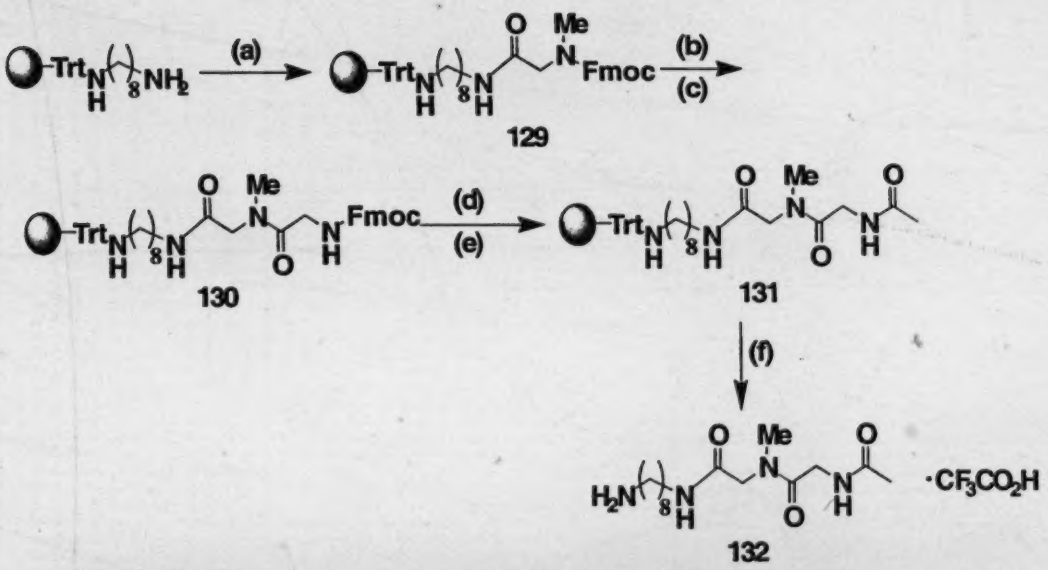


Reaction conditions: $(CH_2O)_n$, *p*-TsOH, Toluene, 110 °C (b) triethylsilane, CF_3CO_2H, $CHCl_3$.

Scheme 2. 10

2.3.2: Model Compound 131 From Fmoc-*N*-Me-Gly-OH

The first synthesis of the desired oligoamines was performed by using Fmoc-*N*-MeGly-OH (Scheme 2.11). This amino acid was coupled to the diaminooctane linker with the aid of HOBt, HBTU, DIPEA, in DMF, as described earlier. The use of 3 equivalents each of the coupling reagents and Fmoc-protected amino acid as well as 6 eq of DIPEA was necessary to ensure complete conversion of the free amine to an amide bond. After several hours of agitation on a shaker, the excess reagents were simply rinsed away and the resin was thoroughly washed with DMF, methanol, and finally DCM. This ensures that there are no further reagents trapped within the solid matrix. As expected, after the reaction was complete, a ninhydrin colorometric assay[51] was negative for the presence of primary amines. Subsequent cleavage of the Fmoc group was achieved by treating the resin with a 20% piperidine/DMF solution for 45 minutes.

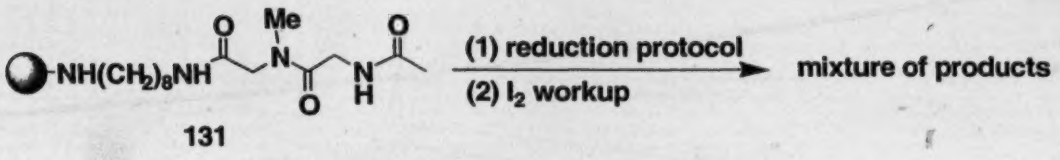


(a) Fmoc-*N*-Me-OH (3 equiv.), HOBt (3 equiv.), HBTU (3 equiv.), DIPEA (6 equiv.), DMF, rt; (b) 20% piperidine/DMF; (c) Fmoc-Gly-OH (3 equiv.), HATU (3 equiv.), DIPEA (6 equiv), DMF; (d) 20% piperidine/DMF, 45 min. (e) Ac_2O, NEt_3, DMF (f) 5% CF_3CO_2H/ CH_2Cl_2

Scheme 2. 11

Coupling of this secondary *N*-methyl amine to Fmoc-Gly-OH was performed with HATU (**91**, described earlier), in DMF, resulting in **130**, as visualized by a negative ninhydrin assay.[51] The Fmoc group was cleaved and the dipeptide was then capped with an acetate group through the reaction of acetic anhydride/triethylamine in DMF to provide the tripeptide **131**. After rinsing and drying, a small sample of the peptide was cleaved from the support using 5% TFA/CH_2Cl_2 to afford the tripeptide **132** as its trifluoroacetate salt.

Although the synthesis of the peptide proceeded smoothly, the reduction step (analogous to reductions previously described) yielded less than desirable results. Even by heating the resin-bound substrate with 30 equivalents of 1 M borane-tetrahydrofuran at 65 °C for 3 days, followed by the usual oxidative workup, full reduction of the triamide substrate was not accomplished. Analysis of a sample of the cleaved product showed a mixture of the mono-amide, di-amide, and the fully reduced tripeptide (Figure 2.5).



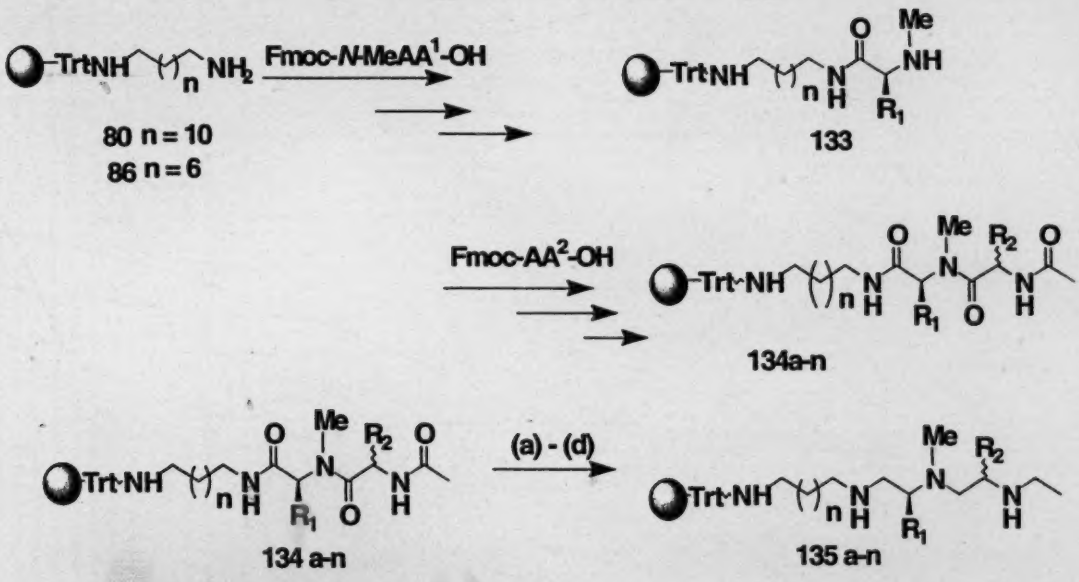
131

Figure 2. 5: reduction of tripeptide 131

Variation of the linker length had no effect on the ability to reduce this linear tripeptide. The linker length was varied to diaminododecane. Again, the synthesis of the peptide proceeded smoothly analogous to that described above. However, the reduction again proved problematic, as with the smaller 8-carbon linker.

It became necessary to vary the amino acid residue in order to determine if all such reductions would be problematic. It must be noted that at the onset of this study the 12 carbon linker was widely employed until the conditions for the more soluble 8 carbon diamine linker were elucidated.

Fortunately, only the case of using an *N*-MeGly-Gly residue as the first two amino acids proved to be a problem, and subsequent syntheses of the linear tripeptides and their corresponding linear triamines could be effectively and efficiently performed. A general scheme toward the synthesis of the resin bound tripeptides via the coupling reactions of α-amino acids is shown in Scheme 2.12. The results for the acetate capped peptides, isolated as their trifluoroacetate salsts, are summarized in the table below (Table 2.2).



Reaction conditions: (a) 1M BH_3·THF, 65 °C, 3 days (b) I_2, AcOH/DIPEA/THF (c) NEt_3/DMF rinses (d) $HO(CH_2)_2OH$, DIPEA, THF, 24 h.

Scheme 2. 12

Table 2.2: Table of Tripeptides 134 and Oligoamines 135

Entry 134 or 135	Linker	Amino Acid [1]	Amino Acid [2]	(a) Yield of peptide (%)	(b) Yield of oligoamine (%)
(a)	86	L-*N*-MeGly-OH	L-Gly-OH	93	mixture
(b)	86	L-*N*-MePhe-OH	L-Ala-OH	76	74
(c)	86	L-*N*-MeAla-OH	L-Ala-OH	75	72
(d)	86	L-*N*-MePhe-OH	D-Phe-OH	94	91
(e)	86	L-Pro-OH	D-Phe-OH	96	73
(f)	86	L-Pro-OH	D-Leu -OH	84	80
(g)	86	L-*N*-MeLeu-OH	D-Leu-OH	90	77
(h)	80	L-*N*-MeAla-OH	L-Ala-OH	97	76
(i)	80	L-*N*-MeGly-OH	L-Gly-OH	84	mixture
(j)	80	L-*N*-MePhe-OH	L-Phe-OH	94	88
(k)	80	L-*N*-MePhe-OH	L-Ala-OH	95	88
(l)	80	L-*N*-MeAla-OH	D-Ala-OH	85	84
(m)	80	L-Pro-OH	D-Phe-OH	97	82
(n)	80	L-*N*-MePhe-OH	D-Phe-OH	86	78

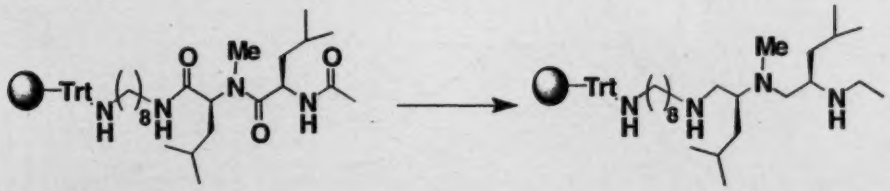
Samples of all of the above peptides were cleaved off the solid-support using 5% TFA in CH_2Cl_2 and were analyzed by ES-MS and ^1H NMR spectroscopy, and in some cases LC-

MS. All of the peptides were determined to be sufficiently pure for the reduction protocol.

In most cases the reduction and work-up of the resulting amine-borane complexes proceeded smoothly under the modified conditions developed. A general scheme for the reduction protocol is shown above.

The yields for the corresponding polyamines **135a-n** are also summarized in Table 2.2 above. In some cases, purification of the oligoamines was performed using semi-preparative HPLC (elution monitored using a UV diode array detector) for characterization purposes. The oligoamines salts that were purified using this method were **135c, e, j, l, m,** and **n**.

An alternative reduction protocol developed by Houghten was also evaluated (Scheme 2.13). This reduction protocol uses a mixture of BH_3, $B(OMe)_3$, and $B(OH)_3$ followed by piperidine treatment of the resin.[65] This alternative protocol, which precluded the use of ethylene glycol, was performed in parallel with our own method on tripeptides **134f, 134g** and **134l** and provided material of comparable purity. It was seen that the use of the I_2 promoted workup, instead of the piperidine workup, gave essentially identical results.



Reaction Conditions: (1) 40 equiv. BH_3·THF, 12 equiv. $B(OMe)_3$, 12 equiv. $B(OH)_3$ 65 °C, 24 h (2) piperidine, 65 °C, 24 h

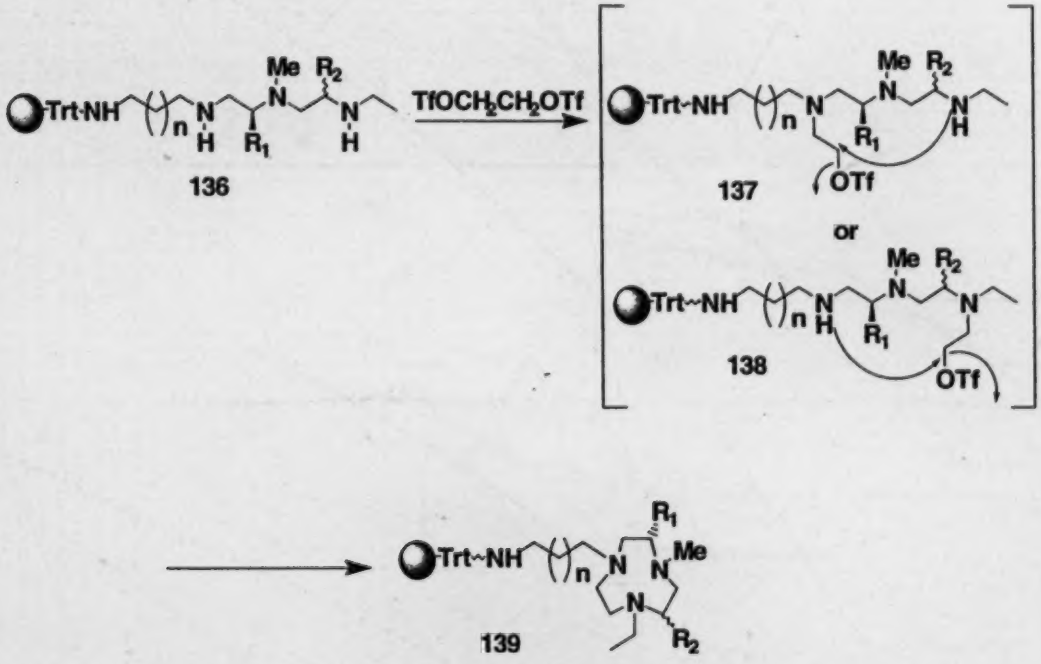
Scheme 2. 13

Thus with the polyamine precursors in hand it was now possible to focus attention on obtaining the desired triazacycloalkanes utilizing a macrocyclization strategy of the corresponding linear triamines on polystyrene solid support. These efforts are described in the next chapter.

3. Synthesis Of Polyazacycloalkanes

3.1: Initial Studies

The synthesis of the triazamacrocycles was based on the observations made by Kim and colleagues.[38] In their work dealing with the synthesis of chiral perazamacrocycles through the opening of cyclic sulfamidates, Kim discovered that slow addition of a dilute solution of a bistriflate to a triamine allowed for the formation of various sized triazamacrocycles. His approach with the bistriflate of ethylene glycol led to the exclusive formation of a dimeric product rather than the 9-membered triazacyclononane. On the other hand, the reaction of the bistriflate of 1,3-propanediol with his triamine precursor yielded exclusively the 10-membered triazacyclodecane. The bistriflate was essential to the reaction and other ethylene glycol derivatives such as the dibromo, bis(*p*-toluenesulfonate) or bismethanesulfonate did not work at all.



Scheme 3. 1

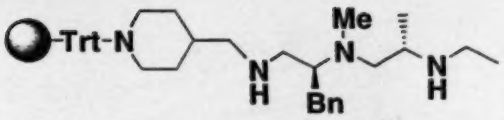
As a result, it was anticipated that if an appropriate amine precursor (such as **136**, Scheme 3.1) could be made on solid-support, the cyclization reaction to afford the 9 or

10-membered triazacycloalkanes would proceed smoothly. It was believed that this strategy toward the triazacyclononanes would be more successful than the corresponding solution phase strategy because of the immobilization of the tetramine **136** precursor on the solid support. Its partial site isolation would thereby reduce the chances of dimerization. Once the first nucleophilic displacement of the bistriflate occurred to give **137** or **138,** the second intramolecular displacement would be favoured over the intermolecular displacement (Scheme 3.1).

The solid-phase approach would also be beneficial because of the ease of product isolation. Excess reagents can be used to drive the reactions to completion, and the resin can be washed by using the different swelling properties of polystyrene in different solvents thereby expunging the unwanted reagents from the resin beads.[52,53] The desired product can then be released from the support by treating the resin with the appropriate cleavage conditions.

With this information it was possible to examine the cyclization of previously synthesized resin-bound oligoamines (**135a-n**). It was noted early on in Kim's synthesis that the central nitrogen in linear triamine **45** (Scheme 1.8, Chapter 1) is a tertiary amine whereas the nitrogen atoms participating in the cyclization are both secondary amines. Our strategy was to develop a general method using resin bound tetramines, derived from Fmoc-protected amino acids, ultimately incorporating functionality and stereogenic centers onto the 'carbon-backbone' of the resulting triazamacrocycle. It became necessary to use an *N*-methylated amino acid as the first residue so that upon reduction of the resulting tripeptide (**134 a-n**, Table 2.2) a tertiary amine residue would result. It was believed that cyclization of these linear precursors could proceed analogously to that of Kim's system.

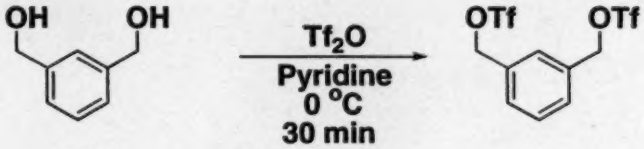
The initial studies began with the formation of the appropriate tetramines. Tetramine **105** (Scheme 2.5, Chapter 2) was the first one synthesized and is shown below (Figure 3.1).



105

Figure 3. 1: resin bound tetramine 105

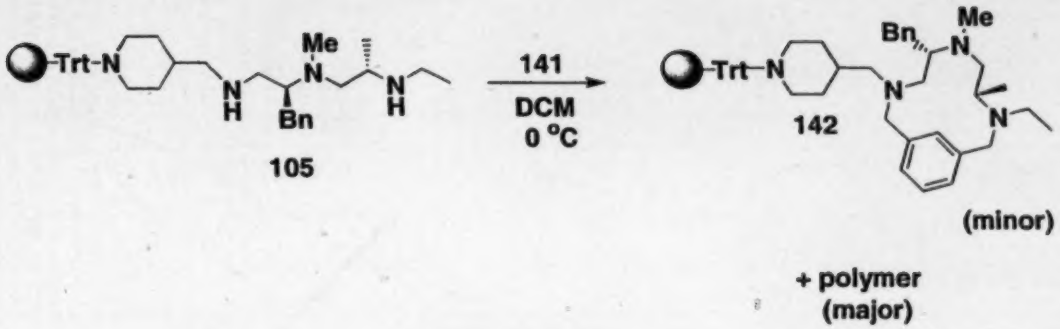
Next, a suitable bistriflate tether was synthesized. Initially, it was decided that the precursor be a rigid species such as the bistriflate of 1,3-dimethanolbenzene. The bistriflate was prepared according to the scheme below (Scheme 3.2).[66] The diol **140** was added slowly to a CH_2Cl_2 solution of the triflic anhydride at 0 °C containing pyridine. The isolation of this bistriflate **141** proved problematic. Any attempt made at concentrating the resultant extract during workup led to rapid decomposition, presumably due to polymerization. To overcome this problem a dilute solution of bistriflate **141** was maintained throughout its use. The subsequent cyclization protocol was performed using this freshly prepared reagent.



140 141

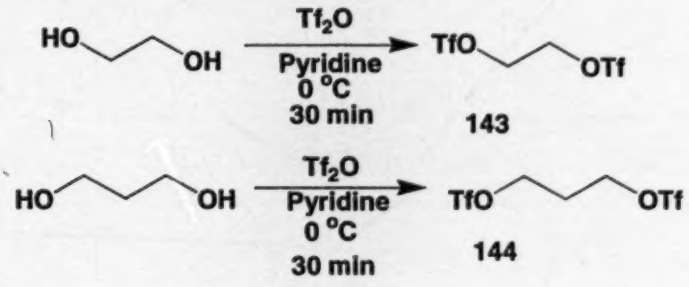
Scheme 3. 2

The cyclization protocol involved the slow addition of a dilute solution of the bistriflate **141** (typically 0.14-0.17 M), *via* a pressure equalizing dropping funnel, to the solution-suspended resin at 0 °C. The addition took place over 6 hours and the solution was stirred for a further 42 hours at room temperature. The resultant suspension was then drained and filtered and the resin dried under vacuum. Unfortunately the major product of this reaction, following cleavage of the resin, appeared to be a polymer. Nonetheless, there was an indication of product **142** formation as seen by electrospray mass spectrometry (Scheme 3.3).



Scheme 3. 3

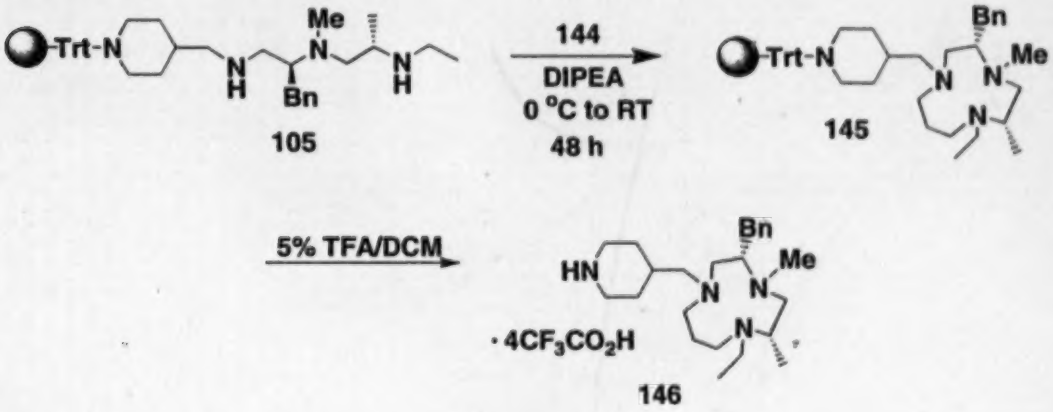
Due to the difficulty of handling bistriflate **141** we decided to examine the stability and ease of handling of the bistriflates of 1,3-propanediol and ethylene glycol (Scheme 3.4). We found that these tethering reagents were substantially easier to work with. The synthesis of **143** and **144** is outlined below. Both compounds were isolated in near quantitative yields based on the starting material and were analyzed by ^{1}H NMR spectroscopy and found to correspond with the literature values.[66]



Scheme 3. 4

The first macrocyclization involved bistriflate **144** and tetramine **105** (Scheme 3.5). Slow addition of bistriflate **144** in CH_2Cl_2, at 0 °C, produced a dark brown suspension. The resulting resin was washed and dried and a small portion was cleaved with a 5% TFA/CH_2Cl_2 solution, thus releasing the free amine as its *tetrakis*(trifluoracetate) salt. It was found that the desired solid-phase transformation took place and generated the triazacyclodecane **145**, upon cleaveage from the resin, which was

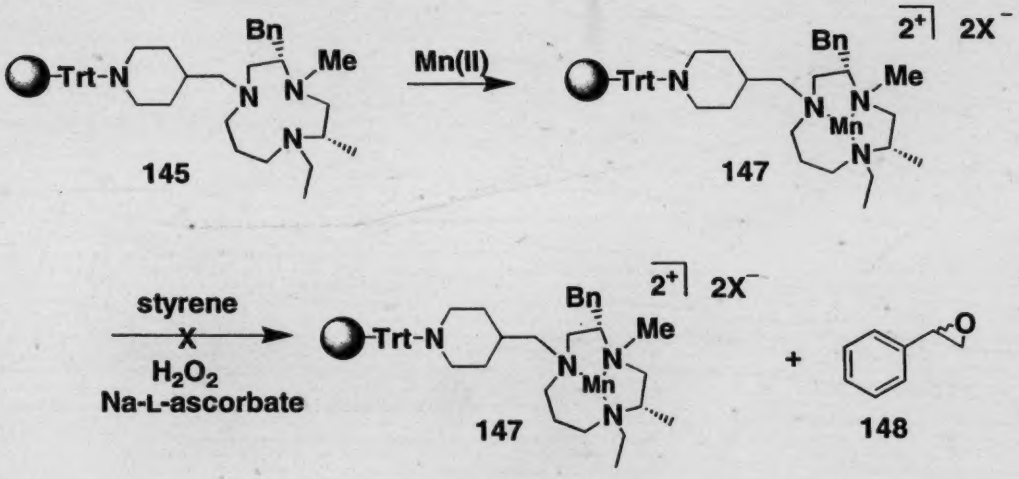
confirmed by electrospray mass spectrometry of cleavage product **146**. An HPLC trace showed a mixture of products. This experiment was carried out prior to our purchase of a semi-preparative HPLC column and thus the mixture of side products could not be eliminated. For this reason ^{1}H NMR and ^{13}C NMR spectroscopic data for the pure compound could not be obtained. Conventional silica gel chromatography methods proved useless as the compounds were immobile on this support.



Scheme 3. 5

Other members of our group have successfully purified trifluoracetate salts of linear polyamines by selective precipitation of the product out of a mixture of methanol/ether. This procedure was attempted unsuccessfully. At this time the possibility of alternate cyclization pathways to yield isomeric products was not considered (*vide infra*).

Manganese binding studies using crude **145** were nonetheless attempted, as well as investigations into the ability of this ligand-metal system to catalyze the epoxidation of styrene to styrene oxide **148**. The resin bound triazacyclodecane **145** was swollen in a mixture of THF/H_2O and a 0.1 M solution of $Mn(OAc)_2 \cdot 4H_2O$ was added followed by vigorous agitation for a period of 20 minutes (Scheme 3.6). Manganese containing resin **147** was then subsequently rinsed very well with a combination of solvents to ensure that any uncomplexed manganese was washed from the polymer.

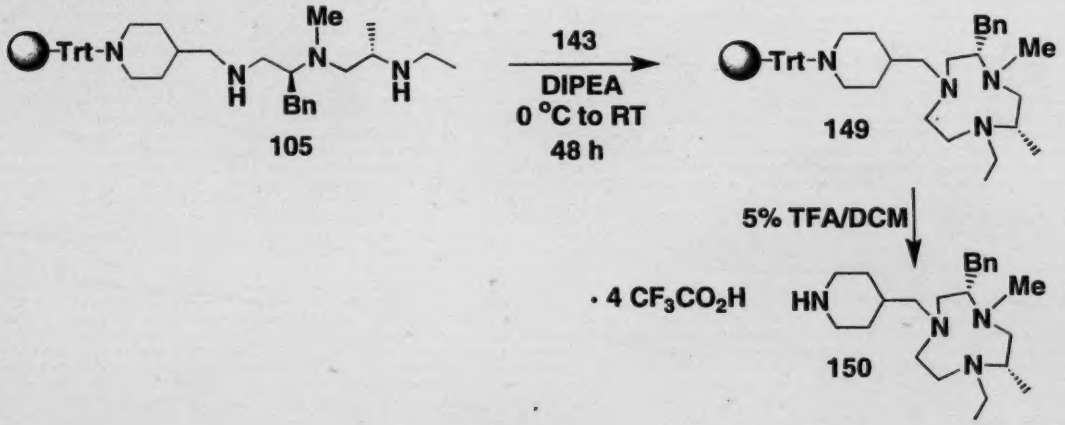


Scheme 3. 6

A qualitative test for manganese(II) was performed[67] using a sodium phosphate/ammonia solution that causes the formation of a pink precipitate of manganese ammonium phosphate $Mn(NH_4)PO_4 \cdot 7H_2O$. Other manganese visualization methods are incompatible with the nature of the tritylpolystyrene solid-support used and would result in the premature cleavage of the substrate from the solid support. Unfortunately, examining the beads under the inverted microscope at different magnifications failed to unambiguously distinguish between a pink precipitate and the natural colour of the polymer beads themselves. Control studies in which a sample of chlorotritylpolystyrene resin was exposed to $Mn(OAc)_2$ solution and then the qualitative test conditions of Na_2HPO_4/NH_3 were equally inconclusive. Nevertheless, we decided to try an epoxidation of styrene under the conditions shown in the scheme above (Scheme 3.6).

To a suspension of the resin in a THF/H_2O solution was added styrene and Na-L-ascorbate (co-ligand). A large excess of H_2O_2 was also added in small portions over several hours. Under these conditions, and those in which Na-L-ascorbate co-oxidant was not used, we did not observe the formation of styrene oxide using this resin-bound triazacyclodecane **145** as ligand. It must be noted that for the triazacyclodecane ligands there are no previously published reports of catalytic epoxidation activity and this area remains largely unexplored.

A second macrocyclization with **105** was attempted. The bistriflate of ethylene glycol (**143**) was used so that the product would be triazacyclononane **150** upon cleavage from the resin (Scheme 3.7).

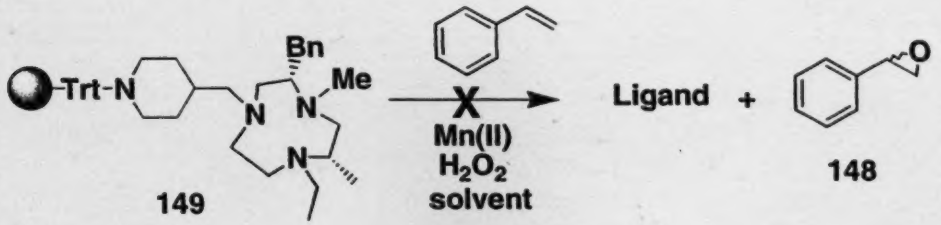


Scheme 3. 7

The bistriflate **143** was added as a dilute solution (typically 0.14-0.17 M) in CH_2Cl_2 to the solution-suspended polymer-bound tetramine **105**. Upon analysis of a cleaved sample of the resin, it was found that the mass of a minor peak in the LC-ES-MS corresponded to the desired product **150** (approximately 35% pure by LC-MS). Again, purification by conventional silica-gel chromatography was impossible because the compound remained adsorbed on the silica. Purification by selective precipitation was also unsuccessful. The possibility of alternate cyclization pathways was not considered at this time and it was thought that the impurities came from the reduction step yielding the tetramine precursor.

Nevertheless, the behaviour of this ligand was explored in a similar manner to the corresponding triazacyclodecane. Inoculation of samples of this resin with $Mn(OAc)_2 \cdot 4H_2O$ and $MnCl_2 \cdot 4H_2O$ were performed. The subsequently well-rinsed resin was treated with a Na_2HPO_4/NH_3 solution in an attempt to visualize if substrate-metal binding was occurring through the formation of a pink precipitate of manganese(II) ammonium phosphate.[67] As with the previous ligand, the similarity between the background bead colour and the precipitate colour the result of this qualitative test proved inconclusive. Attempts were made to use the metal-bound ligand in the epoxidation of

styrene under various conditions. The results of these studies are summarized in the table below (Scheme 3.8 and Table 3.1).



Scheme 3. 8

Table 3.1: Reaction conditions attempted with ligand 149

Conditions*	Metal Source	Result
Styrene, H_2O_2, THF:H_2O 1:1, 0°C, Na-L-ascorbate	$Mn(OAc)_2.4H_2O$	No epoxidation
Styrene, H_2O_2, THF:H_2O 1:1, Na-L-ascorbate Room Temperature	$Mn(OAc)_2.4H_2O$	No epoxidation
Styrene, H_2O_2, DCM:H_2O 2:1, Room Temperature	$Mn(OAc)_2.4H_2O$	No epoxidation
Styrene, H_2O_2, THF:MeOH 1:1, Na-L-ascorbate Room Temperature	$MnCl_2.4H_2O$	No epoxidation
Styrene, H_2O_2, THF:MeCN 1:1, Na-L-ascorbate Room Temperature	$MnCl_2.4H_2O$	No epoxidation

*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 µL; Ligand:metal: = 1.7:1 = 25 µmol: 15 µmol

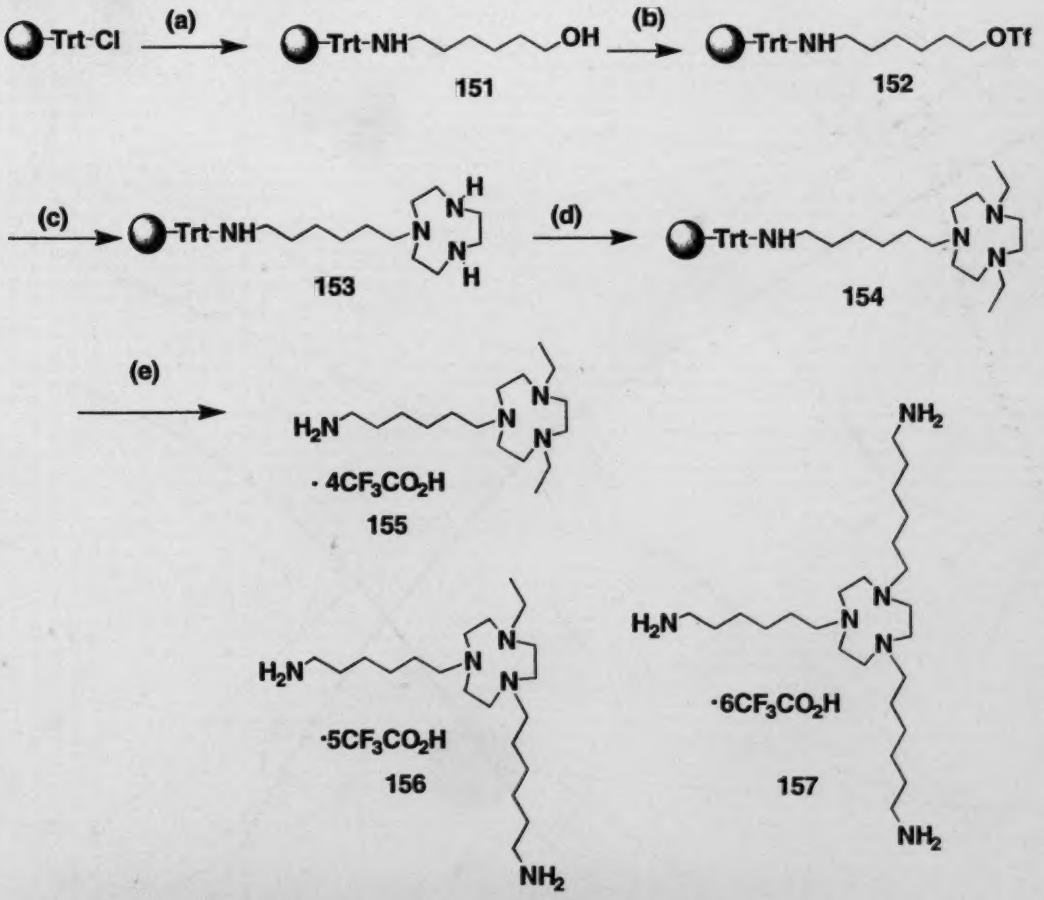
Attempts were made to try to determine by ES-MS whether the ligand was actually binding the metal. A sample of the resin that had been treated with a solution of $Mn(OAc)_2{\cdot}4H_2O$ was cleaved with 5% TFA/CH_2Cl_2 . The solution was concentrated and then dissolved in methanol and injected into the mass spectrometer for analysis. The result of this was the observation of a large MH^+ peak corresponding to **150** and no peaks corresponding to ligand-metal complexes. In retrospect this result is not surprising because protonation of the ligand by TFA, a strong acid, would mean the loss of coordination ability by the ligand and then any complex could be expected to fall apart.

Perhaps in the future a method by which to determine manganese content through trapping of the manganese following cleavage from the resin can be found. One possible method could be to use ion exchange chromatography in which solution after cleavage is passed through a chelating resin to which the manganese becomes complexed. The manganese could then be exchanged with another cation for which the exchange resin has a higher affinity. This quantitative release of manganese could be used to determine both the amount of manganese binding and subsequently the loading of the resin.

Although epoxidation was not observed using the above conditions, the ligand seemed to possess some activity. Indeed, upon addition of H_2O_2, substantial bubbling was observed. This effluence could possibly occur as a result of the disproportionation of H_2O_2 to O_2 and H_2O by the action of the metal-bound ligand.[24] Another problem with this method is that the polystyrene resin is hydrophobic and the conditions required the use of water. A more compatible method would have to be developed. The focus then shifted to the development of prototypical ligand systems on hydrophilic support.

A methodology that could be transferred onto a different polymer matrix was developed using chlorotritylpolystyrene resin. The ease of handling of the polystyrene based resin and the chemistry that had been developed by our group on this support made it an attractive starting point. We envisioned the use of a long linker arm to which we could attach commercially available 1,4,7-triazacyclononane **12** and subsequently derivatize it to yield an unsymmetrical ligand. It was thought that the attachment of a long amino-alcohol through its amine functional group and transformation of the alcohol into a good leaving group for nucleophilic displacement would provide an acceptable model for future studies. The linker that was eventually decided upon was 6-amino-1-hexanol. This was attached to the chlorotrityl polystyrene resin in the usual way giving amino alcohol **151**. The primary alcohol functional group was then transformed into its triflate **152** with triflic anhydride (Scheme 3.9). It was believed that the use of a large excess of 1,4,7-triazacyclononane **12** would allow for the attachment of the triazamacrocycle via one nitrogen atom to yield **153**. In order to determine if cross-linking had occurred it was necessary to reductively alkylate the resulting macrocycle to give **154**. Using the conditions previously developed for the reductive alkylation of oligo(*sec*-amines) it was possible to obtain a mixture of salt products (**155**-

157) of varying mass after cleavage from the solid support. The extent of cross-linking was not determined by quantitative analysis (i.e. LC-ES-MS), but was qualitatively noted by the appearance of peaks in the ES-MS spectrum corresponding to the various triazamacrocycles.



Reaction conditions: (a) (i) 6-amino-1-hexanol, DCM, (ii) MeOH (b) Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine, DCM (c) 1,4,7-triazacyclononane (10 equiv.), THF (d) propionaldehyde, $NaHB(OAc)_3$, DMF (e) 5% TFA/DCM

Scheme 3. 9

Although it was determined that the resin bound triazacyclononane was partially cross-linked, we thought it would still be beneficial to examine the manganese binding properties of these polymer bound ligands. A series of metal binding experiments were

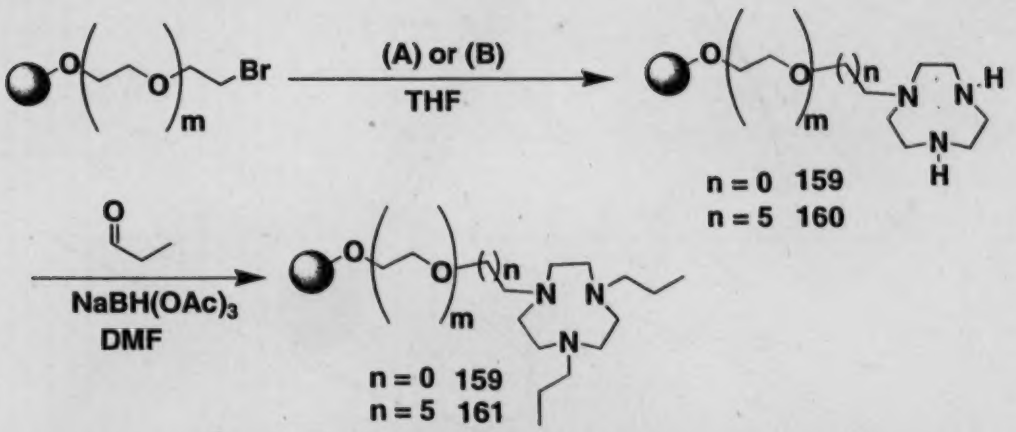
carried out. The subsequently well-rinsed resin was treated with a Na_2HPO_4/NH_3 solution in an attempt to visualize if substrate-metal binding was occurring through the formation of a pink precipitate of manganese(II) ammonium phosphate.[67] Styrene epoxidation experiments were also carried out as previously described. The results of these experiments are summarized in Table 3.2.

Table 3.2: Metal binding and styrene epoxidation conditions with ligand 154

Conditions*	Metal source	Result
Binding study:THF:H_2O (2:1)	$MnCl_2 \cdot 4H_2O$	$Mn(NH_4)PO_4$ precipitate observed
Epoxidation study: MeCN:THF (1:1) Na-L-ascorbate H_2O_2	$MnCl_2 \cdot 4H_2O$	Little epoxide observed
Binding study: THF:MeOH (1:1) 72 h	$MnCl_2 \cdot 4H_2O$	Little $Mn(NH_4)PO_4$ precipitate observed
Binding study: THF: MeOH (1: 1) 72 h	$Mn(OAc)_2 \cdot 4H_2O$	Little $Mn(NH_4)PO_4$ precipitate observed

*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 µL; Ligand:metal: = 1.7:1 = 25 µmol: 15 µmol

Tentagel resin was ultimately selected for the next study. This resin has a polyether backbone and makes it a good choice for use with aqueous systems. The 1,4,7-triazacyclononane **12** was linked to the support in much the same way as described previously (Scheme 3.10). An excess of the triazamacrocycle was reacted with the Tentagel-Br resin in THF. Reductive amination of the subsequent resin-bound ligand gave the propyl-capped triazacyclononane derivative **159**.



Reaction conditions: (A) 12 (B) (i) $NH_2(CH_2)_6OH$ (ii) Tf_2O, pyr, DCM

Scheme 3. 10

Various attempts at styrene epoxidation were performed with this ligand under a variety of different conditions. The results are summarized in the table below (Table 3.3). However, under all conditions examined there was no evidence of epoxide formation. Perhaps there is substantial cross-linking that occurs or that the epoxidation conditions are incompatible with the support. The oligoether backbone of the support itself may play a role in binding of the manganese thereby sequestering it from the triazamacrocyclic cavity. Another possibility is that the polyethylene glycol units of the polymer are themselves being oxidized.

Table 3.3: Styrene epoxidation conditions using ligand 159

Conditions	Metal source	Result
Acetone:THF:H_2O (1:1:1)	$MnCl_2 \cdot 4H_2O$	No Epoxide
THF:H_2O (1:1) Na-L-ascorbate H_2O_2	$MnCl_2 \cdot 4H_2O$	Little epoxide observed
Acetone:THF:H_2O (1:1:1)	$Mn(OAcl_2 \cdot 4H_2O$	No epoxide
THF: H_2O (1: 1) Na-L-ascorbate	$Mn(OAc)_2 \cdot 4H_2O$	No epoxide

*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 µL; Ligand:metal: = 1.7:1 = 25 µmol: 15 µmol

It was thought that perhaps a longer linker was required and that the use of a good leaving group, such as the triflate, would facilitate formation of the macrocyclic ligand. The 6-amino-1-hexanol linker was once again used for this purpose (Scheme 3.10 (B)). After reacting the Tentagel-Br resin with an excess of the aminoalcohol the resulting resin was treated with triflic anhydride in order to convert the primary alcohol to its triflate. Reaction of this resin with an excess of 1,4,7-triazacyclononane **12** provided the solid-support bound triazamacrocycle **160** which was then modified using a reductive alkylation to give **161**. Again, treatment of this resin with a source of Mn(II) followed by a variety of styrene epoxidation conditions (the same as those in Table 3.3) provided no evidence of epoxide formation. This method was subsequently abandoned as it was thought that this solid matrix itself is incompatible with the ability of the ligand to bind metal and to promote olefin epoxidation using H_2O_2 as the oxidant.

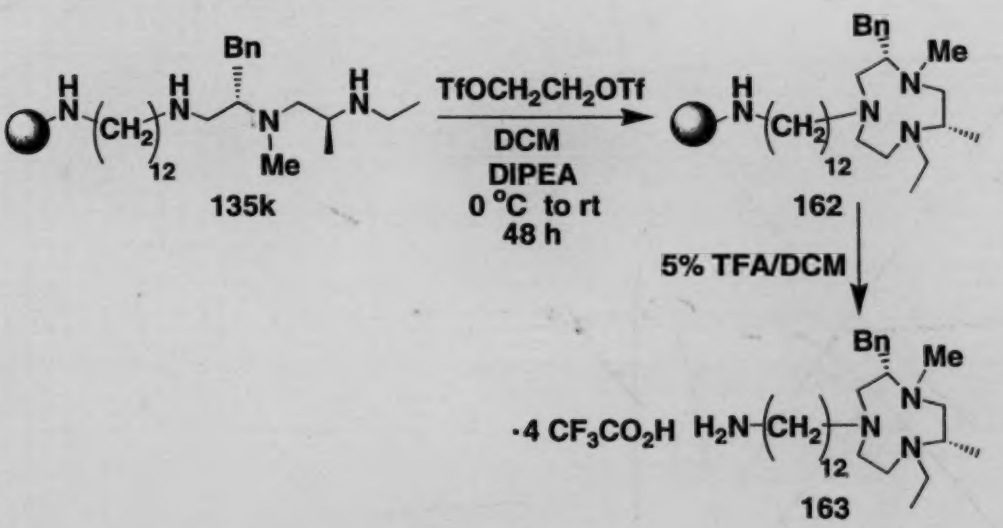
We thought it would be necessary to work out epoxidation conditions in solution first. Once this was accomplished it could then be possible to construct the desired ligand on solid-support, followed by cleavage, and evaluation of its activity in catalytic epoxidation reactions. The ligand that was used for these studies was the commercially available 1,4,7-trimethyl-1,4,7-triazacyclononane **13**.

The study began by reproducing the conditions most frequently used in the literature, those using acetone as the solvent and, $Mn(OAc)_2 \cdot 4H_2O$, and H_2O_2. Acetone as the solvent is known to reduce the disproportionation of the oxidant by the catalyst [24]. It was found that with this catalyst reaction temperature plays an important role in the epoxidation of styrene and that the use of Na-oxalate/oxalic acid as additive was necessary for the efficient formation of epoxide.[40,68] A conversion of >95% for styrene was obtained, which corresponds well with the literature.

The construction of suitable chiral ligands began with the synthesis of oligamine precursors, as described earler, and their cyclization using the appropriate bistriflate tether.

3.2: Synthesis Of Triazacyclononane 163

The described construction of triazacyclononane **163** was achieved using the cyclization strategy seen previously (Scheme 3.11). At the time of constructing this macrocycle the semi-preparative column was not yet available and so purification of this compound was rather difficult. However, the spectral data obtained for the crude material (ES-MS, HRMS and LC-MS), after cleavage of resin **162**, suggested that indeed **163** had been formed as a *tetrakis*(trifluoroacetate) salt. The data suggested that there was a significant amount of 1,12-diaminododecamine **84** present corresponding to the high amount of cross-linking that was problematic in the synthesis of the 1,12-diaminododecyl polystyrene linker **80** (Scheme 2.2, Chapter 2).



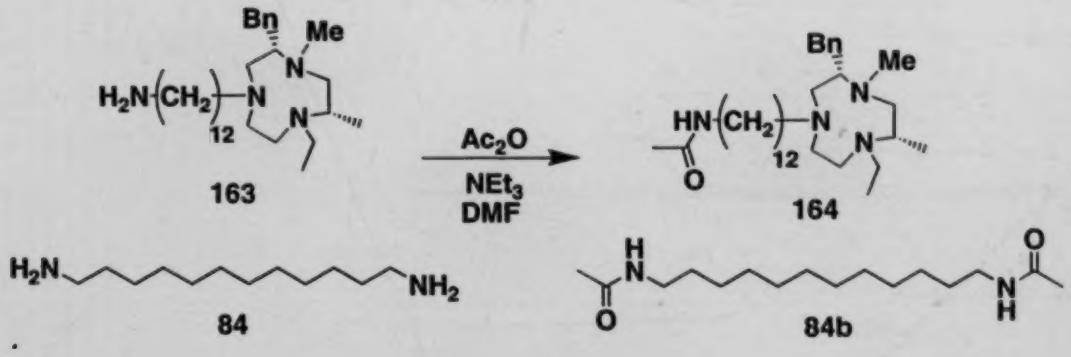
Scheme 3. 11

Post-cleavage derivatization attempts were made to try to find a solution to the diamine contamination problem. It was hoped that perhaps an extraction protocol would be appropriate after acetylation of the primary end. The diamine **84** was expected to be di-acetylated and the triazamacrocycle **163,** only monoacetylated with its three tertiary amine residues. This would allow us to take advantage of a simple acid-base extraction to isolate the desired compound.

Initial attempts were made by studying the behaviour of the model compound, tmtacn **13**. Stirring **13** in a 5% TFA/DCM solution was followed by evaporation and washing of the resultant oil with aqueous NaOH and finally by extraction into ethyl acetate. Confirmation of the extraction protocol was achieved through ES-MS where, after the protocol, a large MH^+ peak was observed corresponding to protonated tmtacn **13**.

This protocol was then repeated with triazacyclononane **163**. First, a control experiment was run where the non-acetylated crude mixture was washed with a 5% aqueous solution of NaOH and then extracted into ethyl acetate. Upon evaporation of the extract, a slightly yellow oil was obtained which, as expected by ES-MS, showed the peaks corresponding to compound **163** and the diamine **84**. However, it was also noted that the yield of **163** after extraction into ethyl acetate was greatly diminished.

The acetylation of the diamine was achieved in the manner shown (Scheme 3.12).



Scheme 3. 12

It was noted that along with the mono-acetylated product, a substantial amount of di-acetylated compound was observed. It was hoped that the extraction protocol would help remove the unwanted impurities from our desired compound.

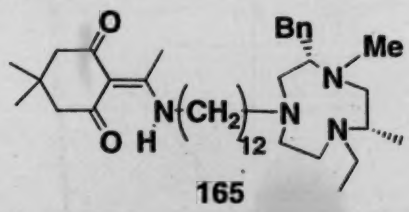
After the extraction protocol it was found that slight purification of **164** was achieved as confirmed by LC-ES-MS, but not enough to make this method practical. Accompanying the extraction of the mono-acetylated compound **164** was a compound

that corresponded to di-acetylated product, as seen by ES-MS. This result was puzzling at the time.

It was also noted that the yield of **164** was low (< 5%). Perhaps this loss is due to the hydrophilicity of **164**. It was then decided that alternate derivatization of the primary amine might make the compound less water soluble and increase the yield after its extraction. The primary amine was therefore modified in two different ways: one by reacting it with pivalic anhydride and the other by reacting it with 2-acetyldimedone.

The use of pivalic anhydride, under the same conditions as in Scheme 3.12, gave results that were similar to those with acetic anhydride; that is mono- and di-acetylation products after extraction. The identity of the di-acetylated product was at that time not determined.

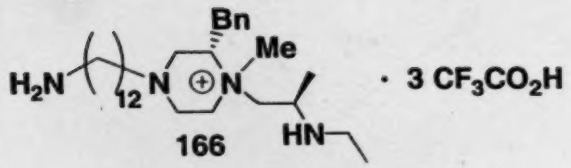
At that time it was not understood why there were two equivalents of these acetylating agents adding on to the molecule along with one equivalent. It was postulated that perhaps one of the nitrogen atoms in the 9-membered ring was for some reason reacting under the reaction conditions. From the work with the 4-aminomethylpiperidine linker it was known that the 2-acetyldimedone protecting group is specific for primary amines over secondary and tertiary ones. Thus, crude compound **163** was treated with 2-acetyldimedone to give mono-protected compound **165** (Figure 3.2).



165

Figure 3. 2: Dde-protected triazacyclononane 165

Here, only the mono-protected compound **165** was observed in the ES-MS after extraction of the crude reaction mixture. It was discovered later that there are actually two major products from this reaction: one corresponding to the desired macrocycle **163** and the other corresponding to a piperazinium ion **166**.



166

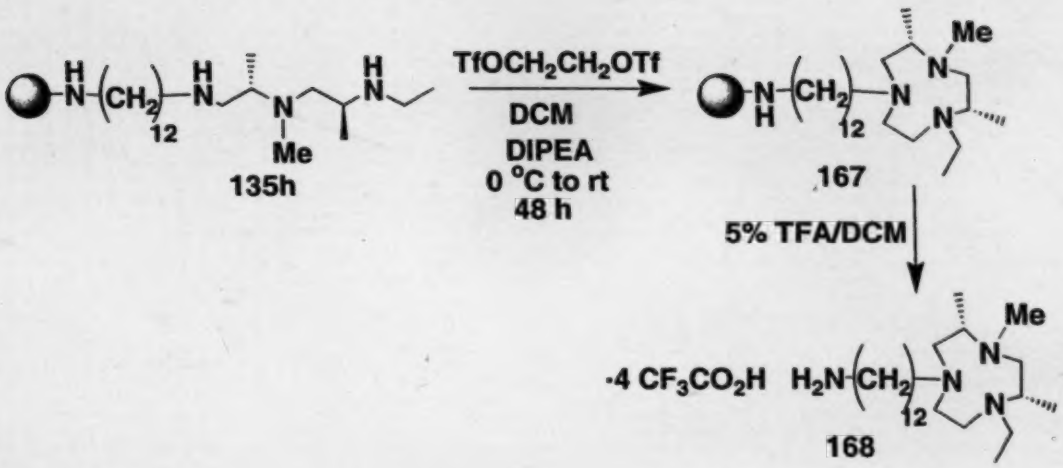
Figure 3. 3: piperazinium ion 166

The 2-acetyldimedone protocol makes sense with what we know because in both the piperazinium ion **166** and the desired triazamacrocycle **163** there is only one primary amine. After extraction, the desired compound **165** would be isolated and the charged piperazinium ion **166** would remain in aqueous solution. As stated, at that time the existence of this piperazinium ion **166** (formed through a competitive cyclization reaction), was not realized. This issue will be discussed later in thorough detail.

Even though bulkier groups were added to compound **163,** it was found that the solubility characteristics did not change significantly and that the compound was still isolated in very low yield (< 5%) making full characterization of these derivatives very difficult.

3.3: Synthesis of triazacyclononane 168

Compound **168** was synthesized according to the procedure outlined above (Scheme 3.13). **168** was obtained as part of a crude mixture containing partially reduced linear tri-, di-, and mono-amines (corresponding to partially reduces **135h**), and 1,12-diaminododecane, by cleaving the resin-bound substrate with 5% TFA/CH_2Cl_2.



Scheme 3. 13

The same problems were encountered with this compound as for the previous triazamacrocycles; namely their purification after cleavage off the resin. Crude product **168** was acylated using pivalic anhydride in the presence of triethylamine and DMF giving a mixture of mono-acetylated triazacyclononane **169**, a substantial amount of the di-acetylated 1,12-diaminododecane, and unknown compounds as seen by LC-MS (**169** approximately 60% pure).

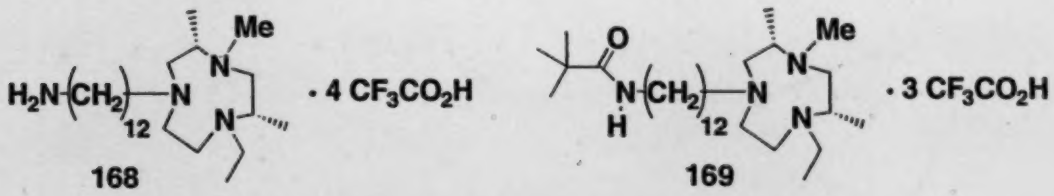


Figure 3. 4: triazacyclononane 168 and derivative 169

In this case only the mono-acylated compound **169** was observed by ES-MS. Perhaps without the phenylalanine residue, the compound preferentially cyclizes to form the 9-membered ring instead of the corresponding piperazinium ion.

Epoxidation of styrene was attempted using both the crude mixture containing **168,** the acetylated **169** and resin-bound compound **167**. The results for these experiments are summarized in Table 3.4.

Table 3.4: Styrene epoxidation experiments with ligands 167, 168, and 169

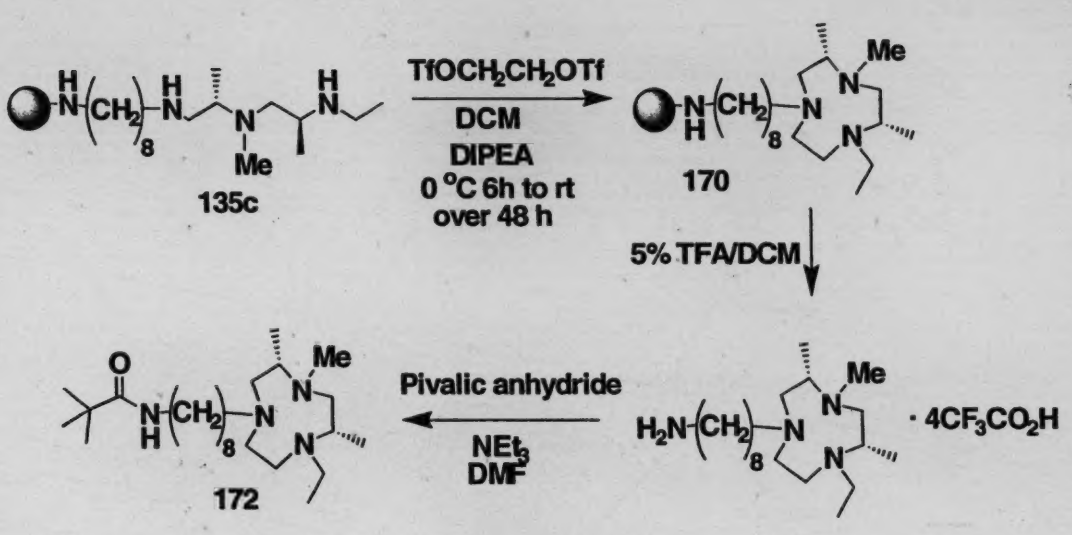
(entry) Compound	Conditions*	Result
(a) **169**	Styrene/Acetone/0 °C/Na-oxalate-oxalic acid/ $Mn(OAc)_2 \cdot 4H_2O/H_2O_2$	No epoxidation observed
(b) **167**	Styrene/1:1 acetone:DCM/ 0 °C/ Na-oxalate-oxalic acid/ $Mn(OAc)_2 \cdot 4H_2O/H_2O_2$	No epoxidation observed
(c) **168**	Styrene/0 °C/acetone/$Mn(OAc)_2 \cdot 4H_2O$/ NEt_3/H_2O_2	No epoxidation observed
(d) **168**	Styrene/0 °C/acetone/$Mn(OAc)_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid/ H_2O_2	No epoxidation observed

*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 µL; Ligand:metal: = 1.7:1 = 25 µmol: 15 µmol

The above results were initially discouraging. It appears likely that either the ligand itself was not suitable for binding manganese metal, or, that upon binding the complex has a much higher rate of peroxide disproportionation than epoxide formation. To support this hypothesis a significant amount of gas was evolved upon addition of hydrogen peroxide to each of the experiments summarized in Table 3.3. Another possibility is that cross-linking of the resin, due to the problems encountered with the 1,12-diaminododecane linker, was interfering with the reaction. As a result, the synthesis of the analogous 1,8-diaminooctanyl polystyrene resin was performed.

3.4: Synthesis Of Triazacyclononane 172

The synthesis of **170** was carried out as previously described (Scheme 3.14). The free ligand **171** was liberated upon cleavage of the resin using 5% TFA/CH_2Cl_2, giving a crude mixture containing **171** as its *tetrakis*(trifluoroacetate) salt.



Scheme 3. 14

Treatment of this crude mixture with pivalic anhydride in the presence of triethylamine in DMF afforded **172** as confirmed by LC-MS, although in low purity. However, only the mono-acetylated compound was observed. The possibility of piperazinium ion **173** formation was not considered at this time because of these results (Figure 3.5).

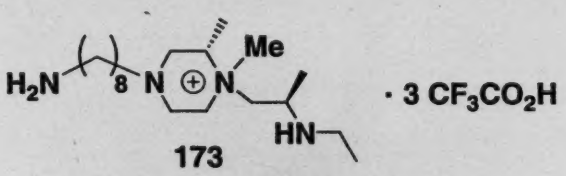


Figure 3. 5: piperazinium ion 173

Purification of the resultant triazamacrocycle **172** proved to be difficult. Extraction protocols resulted in the isolation of **172** in very low yield. Attempts at precipitation from hexanes did not improve the purity of the desired compound as the impurities precipitated out as well.

However, various attempts were again made at epoxidation of styrene with **170-172**, using a number of conditions, summarized in the table below (Table 3.5).

Table 3.5: Styrene epoxidation conditions using ligands 170, 171, and 172

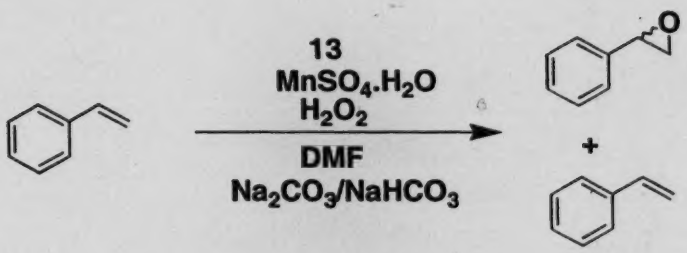
(entry) Compound	Conditions*	Result
(a) **170**	Styrene/ $MnCl_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid/MeCN/ 0 °C/NEt_3/H_2O_2	No epoxidation
(b) **170**	Styrene/ $MnCl_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid/ MeCN/ 0 °C/H_2O_2	No epoxidation
(c) **170**	Styrene/CH_2Cl_2/$MnCl_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid / 50 °C/H_2O_2	No epoxidation
(d) **170**	Styrene/$MnSO_4 \cdot H_2O$/Na_2CO_3-$NaHCO_3$(pH≅ 8.0)/DMF/H_2O_2	Ratio of styrene:styrene oxide = 1:0.7
(e) **171**	Styrene/$MnSO_4 \cdot H_2O$/Na_2CO_3-$NaHCO_3$(pH≅ 8.0)/DMF/H_2O_2	Ratio of styrene:styrene oxide = 0.38:1.00
(f) **172**	Styrene/acetone/$MnCl_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid/0 °C/H_2O_2	No epoxidation

*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 μL; Ligand:metal: = 1.7:1 = 25 μmol: 15 μmol

The addition of triethylamine to the reaction medium in (a) seemed to have a negative effect on the progress of the reaction, with the observation of a distinct colour change (dark brown) to the resin and the evolution of gas. The results for (c) can perhaps be attributed to the use of immiscible solvents and the high reaction temperature that may favour disproportionation of the oxidant. It is difficult to propose why the conditions in (f) did not allow epoxidation, however, it could be that the manganese-ligand complex was not formed. In the cases of (d) and (e) the results were obtained by using a procedure as described by Burgess[69] in which $MnSO_4$ in DMF was used, in a bicarbonate buffer at pH 8, for the catalytic epoxidation of olefins with H_2O_2. A wide variety of olefins were compatible with this procedure, including styrene and styrene derivatives, and trisubstituted aliphatic alkenes. However, terminal aliphatic alkenes did not yield the corresponding epoxides. The ratios, for the experiments summarized above, were determined by ^1H NMR spectroscopic analysis. The experimental conditions of (e) were repeated using **163** with a similar result (styrene: styrene oxide = 1:0.86). Further studies were conducted in order to determine the catalytically active species.

Several control experiments were carried out. In light of the results of (e) and (f) (Table 3.5) the first control experiment involved the use of

1,4,7-trimethyl-1,4,7-triazacyclononane **13** under the conditions used by Burgess (Scheme 3.15).[69]



Scheme 3. 15

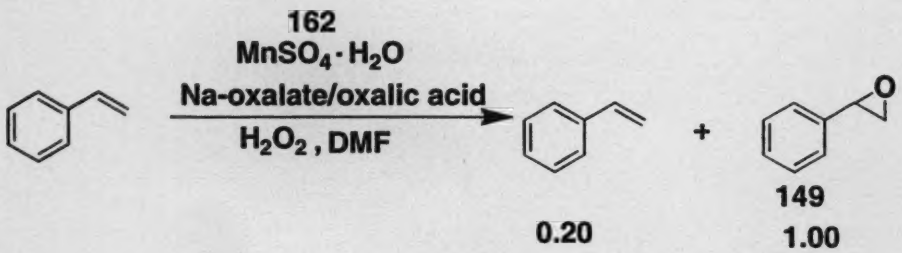
The ratio of styrene to styrene oxide, as determined by ^{1}H NMR spectroscopy, was 1:0.23. This experiment yielded less epoxide than reported by Burgess without the use of the tmtacn ligand **13**. A repeat of this reaction using identical conditions to those of Burgess gave a similar result to the reported one. It was thought that under the reaction conditions, the tmtacn-Mn(II) complex could actually be decreasing the yield of the epoxide, due to its capacity to promote the disproportionation of hydrogen peroxide, rather than increasing it with its epoxidation acitivity. Burgess did state that the use of a bicarbonate/carbonate buffer was crucial for the epoxidation reaction and that the postulated HCO_4^- (percarbonate) ion combines with manganese to form the active species *in situ*.

In order to test this theory and to develop conditions under which triazacycloalkane ligands could be used, the buffer was altered, maintaining the same pH, and the effect of the use of tmtacn **13** was tested by its inclusion or exclusion from the reaction medium. Using conditions as above (Scheme 3.15), but changing the buffer system from a carbonate/bicarbonate buffer to a phosphate buffer, a ratio of styrene to styrene oxide of 1:0.08 was observed by ^{1}H NMR spectroscopy. It was expected that some epoxidation would occur in this reaction because of the presence of tmtacn **13** but the phosphate buffer may have a negative effect on the binding of the metal to form the tmtacn-Mn(II) complex necessary for epoxidation. Changing the buffer to a phosphate buffer and omitting tmtacn **13** from the reaction gave essentially no observable epoxide formation. These results suggest that an additive is essential for epoxidation to occur and

that in Burgess' system the bicarbonate/carbonate buffer is playing the essential role even in the presence of the tmtacn ligand **13**.

It was known from previous work in the literature that a sodium oxalate/oxalic acid buffer was a good additive for these types of complexes.[68] Control experiments on the epoxidation of styrene were performed using this buffer at around neutral pH, $MnSO_4 \cdot 2H_2O$, hydrogen peroxide and the tmtacn ligand **13**. The results showed a ratio of styrene:styrene oxide of 0.53:1. This was an improvement over the observed result in the absence of this co-oxidant. Other experiments were conducted to determine if the tmtacn **13** was necessary in this system in light of the results obtained by Burgess. It was found that when styrene was incubated under the above conditions in the absence of tmtacn **13** essentially no epoxidation was observed.

With this information, a re-examination of the epoxidation of styrene, using resin-bound ligand **162** under the above conditions, with DMF as solvent (Scheme 3.16) was carried out. The isolation of styrene oxide **148** with DMF as the solvent is relatively facile as during the workup water can be added to partition the DMF, and styrene oxide can then be extracted into pentane. The use of the resin-bound ligand **162** was also desirable as when the reaction reaches completion **162** can simply be filtered off and washed, leaving the desired epoxide in solution and the ligand still attached to the solid-support.



Scheme 3. 16

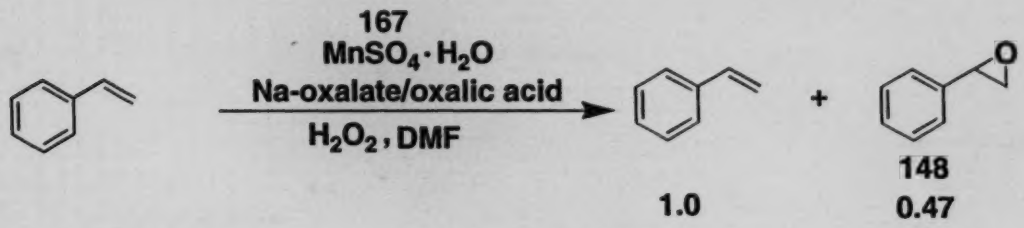
As shown above (Scheme 3.16), the epoxidation under these new modified conditions proceeded well, generating a ratio of styrene to styrene oxide of 0.20:1, as determined by ^1H NMR spectroscopy, representing a conversion of 83%. Attempts to determine if the reaction had proceeded with any enantiomeric selectivity were carried

out by analyzing a small amount of the crude mixture on a chiral HPLC column (CHIRACEL OD, 0.46 cm I.D. × 25 cm, 0.25 ml/min. flow rate, 30% isopropanol/water). Results showed that the reaction proceeded to give a racemic mixture. Nevertheless, this was considered to be an encouraging result due to the high conversion obtained.

An attempt was made to recycle resin **162** in another epoxidation reaction of styrene after the appropriate washing steps. By proceeding in exactly the same manner as described above it was found that the final ratio of styrene to styrene oxide was 1:0.02, suggesting that the catalytic activity of the ligand had been destroyed during its use in the previous reaction. Resynthesis of the ligand from the corresponding resin-bound linear tetramine **135k** was carried out in order to repeat the experiment. Upon obtaining ligand **162** the epoxidation of styrene was repeated. However, on this occasion the ratio of styrene to styrene oxide dropped significantly from the first trial giving a ratio of 1:0.10. It is unknown whether the difference of reactivity between the two batches of resin had to do with purity of the ligand, as only the purity of this second batch was determined (about 60% by LC-UV-ES-MS). The reaction conditions described in the literature use the ligand in excess, which in light of the purity assessment of the ligand, was not the case in the experiments using the second ligand batch. The purity, as determined by LC-MS, did not at this time consider the formation of the quaternary piperazinium ion **166** because the phenomena was still unknown to us. All of the obtained spectral data, including LC-MS, pointed toward one product from the cyclization reaction. Therefore it seems highly likely that an excess of manganese was used with respect to ligand **162**. This is one possible explanation as to why the yield of epoxide with the second batch of resin was lower. This does not, however, explain the high ratio of styrene oxide in the first reaction and the apparent lack of formation of significant amounts of the piperazinium ion **166**. Decreasing the amount of manganese used did improve the ratio of styrene to styrene oxide, but only to 1:0.20. These experiments were repeated for the second batch of resin under the same conditions except that the reaction mixture was cooled to 0 °C prior to addition of hydrogen peroxide. Again, with this batch, a maximum ratio of styrene to styrene oxide of 1:0.10 was achieved.

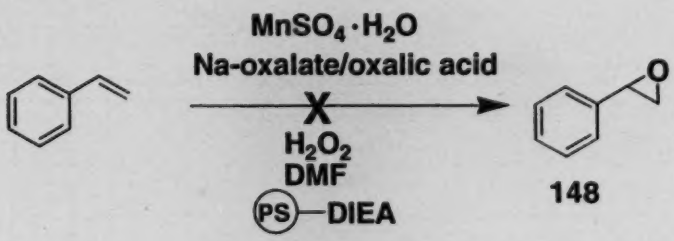
Epoxdiation reactions with resin-bound triazacyclononane **167** were also reinvestigated (Scheme 3.17). The first attempt at epoxidation met with failure due to

technical difficulties (stir plate stopped stirring). Workup of the reaction mixture and analysis by ^{1}H NMR spectroscopy showed only trace amounts of the epoxide. However, once the technical difficulties were overcome the reaction was repeated at room temperature and a ratio of styrene to styrene oxide of 1:0.47 was observed. An analysis of the crude reaction products by chiral HPLC (CHIRACEL OD, 0.46 cm I.D. × 25 cm, 0.25 ml/min. flow rate, 30% isopropanol/water) again showed that a racemic mixture was produced. Repetition of the reaction with this previously used resin sample containing **167** led to no observed formation of styrene oxide, indicating a loss of reactivity.



Scheme 3. 17

The possibility arose that various nitrogen containing species, such as a mixture of amines (from the incomplete reduction by BH_3) that were still attached to the solid support, could be responsible for catalyzing the epoxidation reaction. In order to rule out this possibility, control experiments were conducted with polystyrene-diisopropylethylamine as the solid support (PS-DIEA). The ratio of Mn(II):DIEA, based on resin substitution, was varied in these experiments. In all cases, no epoxidation was observed (Scheme 3.18).



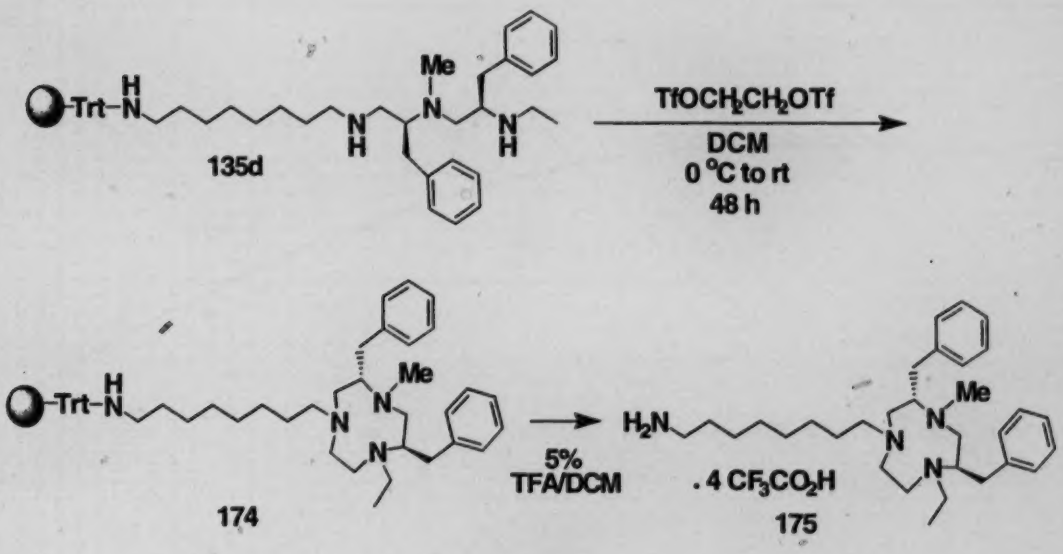
Scheme 3. 18

At the same time, the background reaction in a polystyrene-divinylbenzene matrix was determined by using the epoxidation conditions in the presence of non-derivatized polystyrene 1% divinylbenzene co-polymer. The amount of manganese used was also varied in these studies. The ratio of styrene to styrene oxide was determined to be 1: 0.02, that is, a negligible formation of epoxide.

The synthesis of a variety of these triazacycloalkane ligands continued using a number of different L and D amino acids.

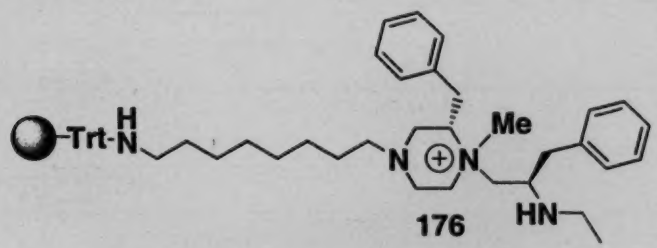
3.5: Synthesis Of Triazacyclononane 175

In previous experiments it was observed qualitatively that amides containing a phenylalanine residue gave better results in the reduction step than ones containing only aliphatic amino acid residues. It was also believed, by examining molecular models, that the use of an L and a D amino acid for the formation of the triazamacrocycle could afford a cavity that would be predisposed for forming a chiral product in the epoxidation step. To determine whether this was the case, tiazacyclononane **174** was constructed (Scheme 3.19).



Scheme 3. 19

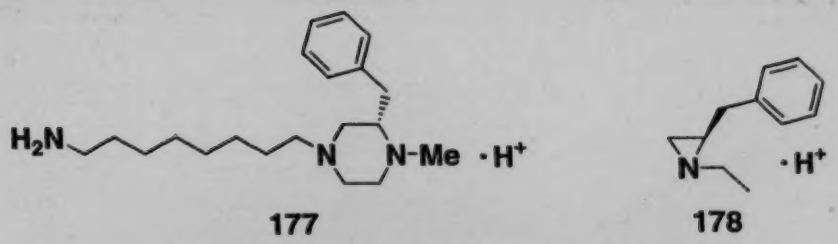
However, upon careful examination of several LC-MS traces of **175**, obtained by varying the conditions over a wide range of solvent mixtures, it was seen that the peak which had previously been thought to be a single peak, and hence one compound, was actually composed of two very closely spaced peaks, and therefore two different compounds. Variation of the LC-MS conditions eventually led to the separation of the two peaks on an analytical column giving the products in a 7:3 ratio. The masses of the two peaks, as determined by ES-MS, were identical, both with an $[MH]^+$ of *m/z* 479, which is one reason why this had been overlooked in the previous cases. Initially it was believed our reaction conditions promoted epimerization at one or more centers leading us to believe that the two peaks were diastereomers of each other. Re-examination of the data for the other crude mixtures of triazamacrocycles showed that this was in fact a generally observed phenomenon. The identity of the second peak was only realized when the fragmentation pattern of each was studied. Although ES-MS is a very mild ionization method, Hoffmann elimination, and other fragmentations of quaternary ammonium compounds, is a facile process.



176

Figure 3. 6: piperazinium ion 176

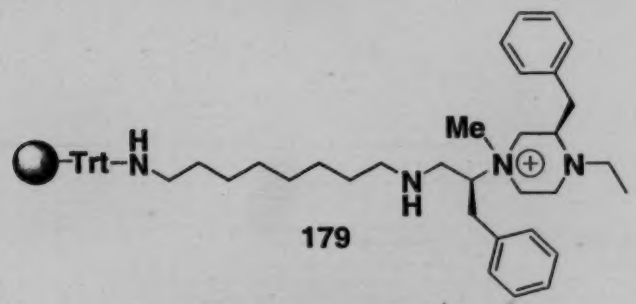
The structure of the product was subsequently determined to be **176**, shown above (Figure 3.6). Characteristic peaks were found to occur in the fragmentation pattern of this piperazinium ion **176** in the ES-MS and these are shown below (Figure 3.7). The masses of the fragment peaks were *m/z* 318 for **177** and *m/z* 162 for **178**.



177 178

Figure 3. 7: ES-MS fragments 177 and 178

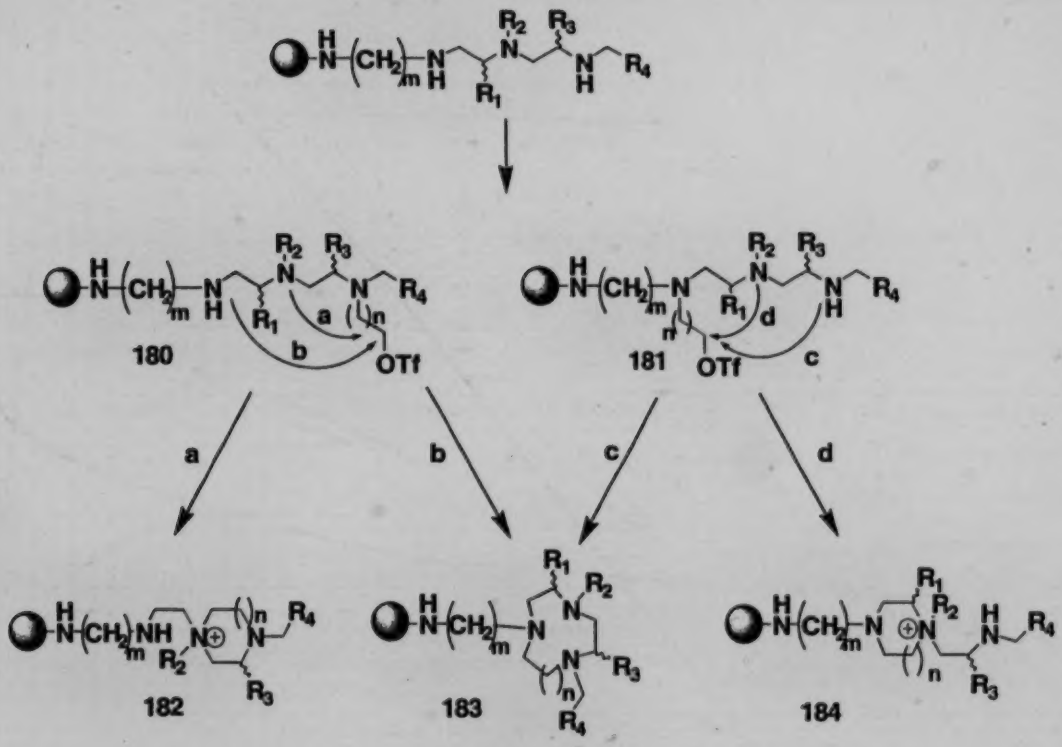
It is particularly interesting to note that only the fragmentation pattern for this particular product **176** was observed and that the expected fragmentation pattern from the other possible piperazinium product **179** (Figure 3.8) was not observed.



179

Figure 3. 8: piperazinium ion 179

We tentatively propose that **176** originates from the first alkylation intermediate **181** originating from attack of the bistriflate at the least hindered secondary amine (path (d) as shown below) (Scheme 3.20).[70]

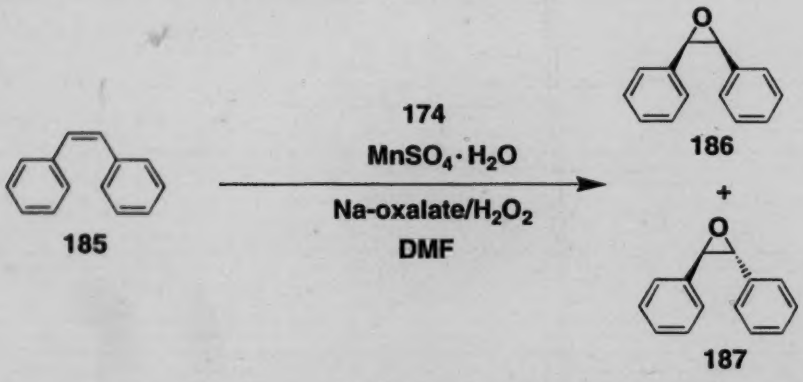


Scheme 3. 20

The resin-bound compound **174** was tested for its catalytic epoxidation properties, even though it contained the piperazinium ion impurity, under the experimental conditions described earlier. It was found that the ratio of styrene:styrene oxide was 1:0.90. Analysis of the crude product mixture by chiral HPLC again showed a racemic mixture (CHIRACEL OD, 0.46 cm I.D. × 25 cm, 0.25 ml/min. flow rate, 30% isopropanol/water). Some of the resin-bound substrate was cleaved from the resin and extracted (H_2O/EtOAc/ pH > 10) to afford the free triazacyclononane **175** along with the piperazinium ion **176**. This mixture of compounds was then used in the epoxidation of styrene. The epoxidation gave styrene to styrene oxide in a ratio of 0.11:1. However, although this conversion is very good, analysis by chiral HPLC again showed a racemic mixture of styrene oxide.

An examination of the epoxidation of *cis*-stilbene **185** ensued to determine if a mixture of *cis*-stilbene oxide and *trans*-stilbene oxide (Scheme 3.21) would be obtained

under these epoxidation conditions. A mixture of products would provide evidence for a mechanism that involves the racemization of a benzylic radical.



Scheme 3. 21

The ratio of *cis*-stilbene oxide **186** to *trans*-stilbene oxide **187** was determined by ^{1}H NMR to be approximately 1:2. It was also found that there was a substantial amount of starting material left (ratio of 1:0.20) as compared to products.

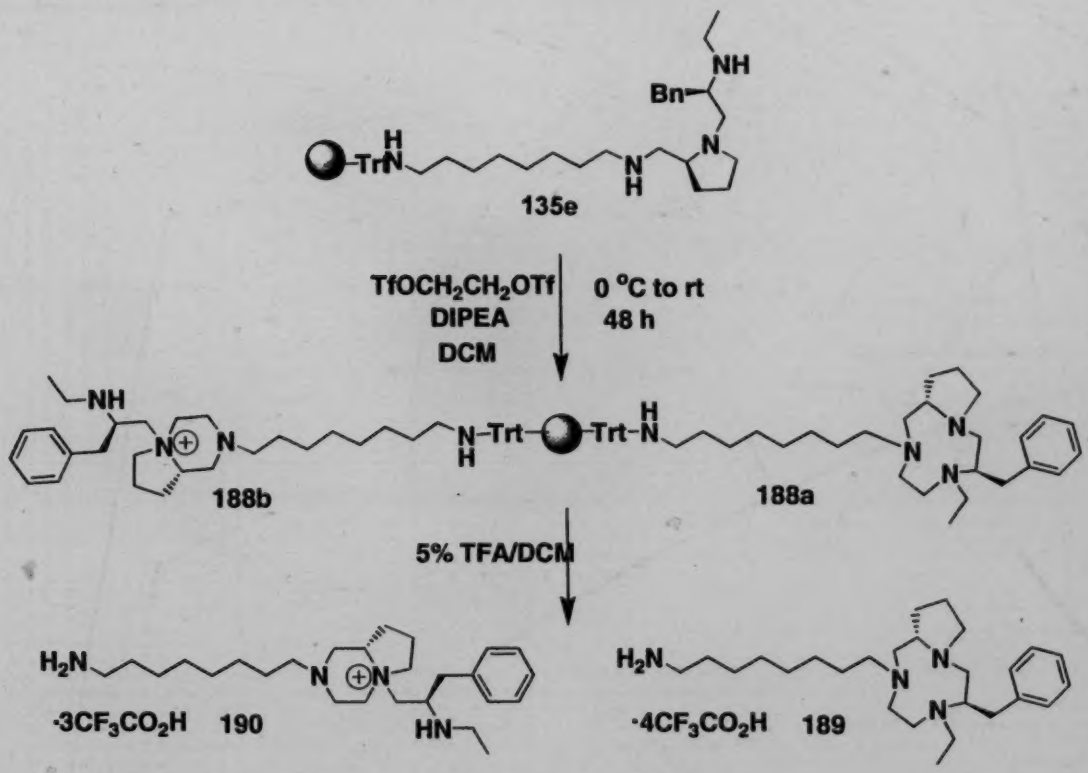
Although the triazacyclononane **174** could be formed, the characterization of the cleaved compound **175** was very difficult due to the contamination with the piperazinium adduct **176**. The inefficient extraction protocol did not yield sufficient material to obtain ^{13}C NMR spectroscopic data.

It became necessary to cleave the products from the resin and then purify the crude mixture using chromatographic methods. Initially it was believed that silica column chromatography would work, but it was quickly discovered that purification of these *tetrakis*-trifluoroacetate salts was impractical using standard column chromatography techniques due to their immobility under these conditions. Purification using a semi-preparative HPLC column, containing the same support (C8 reverse-phase) as the analytical column used to separate the compounds for analytical analysis was considered to be the most appropriate method for purification. With this larger column the analytical conditions [2% MeCN (0.1% TFA)/98% H_2O (0.1% TFA) to 50% MeCN (0.1% TFA)/50% H_2O (0.1% TFA) over 12 minutes, and maintained at the latter ratio for a further 8 minutes)] could be modified and applied to bigger sample volumes for

isolation of the desired components, by simply increasing the flow rate. Thus compound **174** was purified and isolated in sufficient yield for characterization.

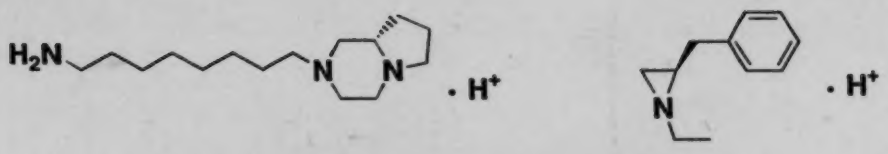
3.6: Synthesis of Triazacyclononane 189

The synthesis of resin-bound compound **188** proceeded as previously described (Scheme 3.22), and released the desired triazacyclononane salt, **189,** after cleavage from the resin, and the unwanted piperazinium ion **190** in a ratio of 2.5:1.



Scheme 3. 22

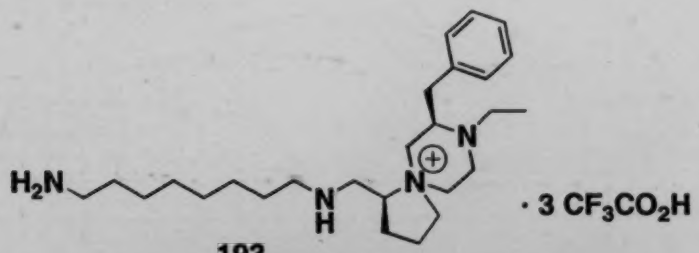
The identification of the piperazinium adduct **190** was similar to that of compound **176**. The ES-MS spectra provided a fragmentation pattern for one of the peaks corresponding to expected fragment sizes for the proposed piperazinium adduct **190**, with masses of *m/z* 254 for fragment **191** and *m/z* 162 for fragment **192** (Figure 3.9).



191 192

Figure 3. 9: ES-MS fragments 191 and 192

Again the fragmentation pattern for the other possible piperazinium ion **193** (Figure 3.10) was not observed.

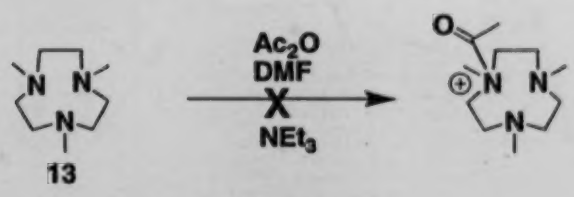


193

Figure 3. 10: possible piperazinium adduct 193

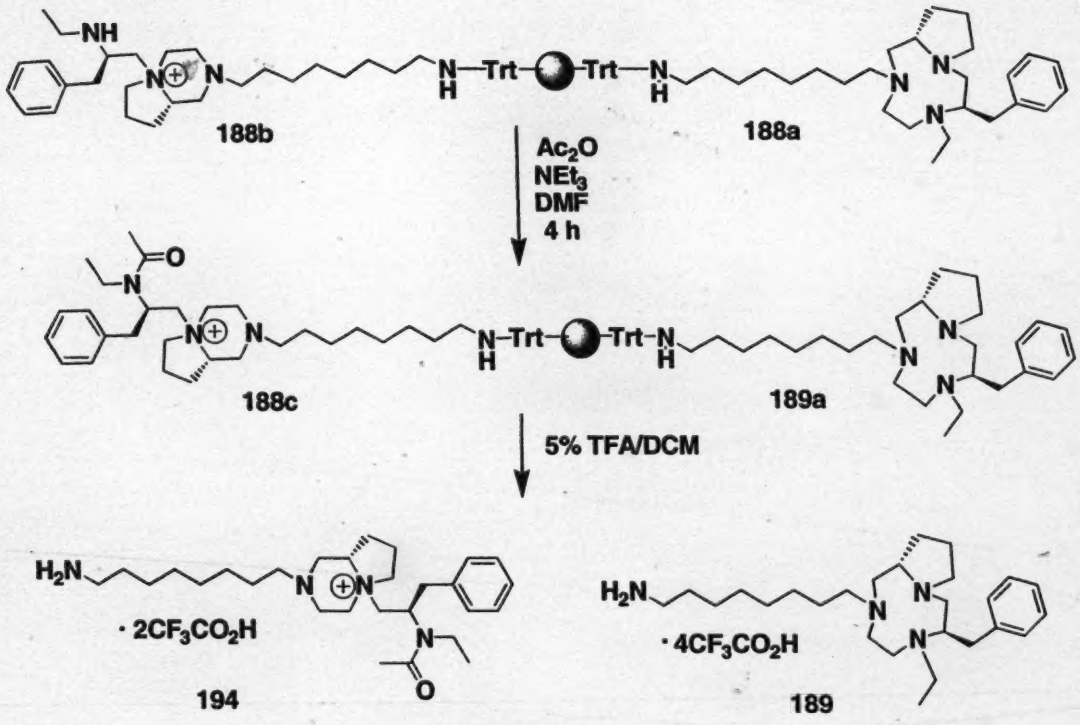
It was considered necessary to unambiguously establish that the desired triazacyclononanes were formed, in lieu of epoxidation data. Epoxidation experiments of styrene in which the desired epoxide had been formed were hitherto used as indirect proof that the desired triazacyclononane was being produced. However, this method did not establish which peak in the analytical LC-MS was the desired product and which was the piperazinium ion, even though the above fragmentation pattern was observed. An alternate chemical method was more desirable to produce a mass difference between the two compounds, along with the use of the LC-MS trace to determine which peak would change retention times and mass, and which peak would remain unaffected. An examination of the structures of the triazacyclononane product **189** and the piperazinium ion side product **190** revealed that it should be possible to acetylate the piperazinium ion at its secondary amine while on the solid support, producing a tertiary amide, and that the desired triazamacrocycle should not be acetylated in this solid-phase reaction.

Control experiments using the commercially available tmtacn ligand (1,4,7-trimethyl-1,4,7-triazacyclononane) **13** were conducted to determine if the tertiary amines within the macrocycle had any tendency to quaternize with the envisaged capping protocol employing acetic anhydride/triethylamine/DMF. To our satisfaction, even with a large excess of acetic anhydride, and running the reaction overnight, tmtacn **13** had no tendency for acetylation (Scheme 3.23).



Scheme 3. 23

The resin-bound compounds **188a** and **188b** (triazacyclononane and piperazinium ion) were subjected to the acetylation conditions by treating the resin with acetic anhydride/triethylamine in DMF (Scheme 3.24).



Scheme 3. 24

It was found that upon cleavage of this resin sample, and analysis by analytical LC-UV-MS, the first peak eluted from the column with a retention time of 12.0 min, remained unchanged with a mass of *m/z* 415 and that the second peak disappeared and a peak corresponding to acetylated derivative **194** appeared. Notably, this new peak also displayed a similar fragmentation pattern to its non-acetylated counterpart losing analogous fragments as seen in the mass spectrum. The crude LC-MS trace for this result is shown below (Figure 3.11a and b).

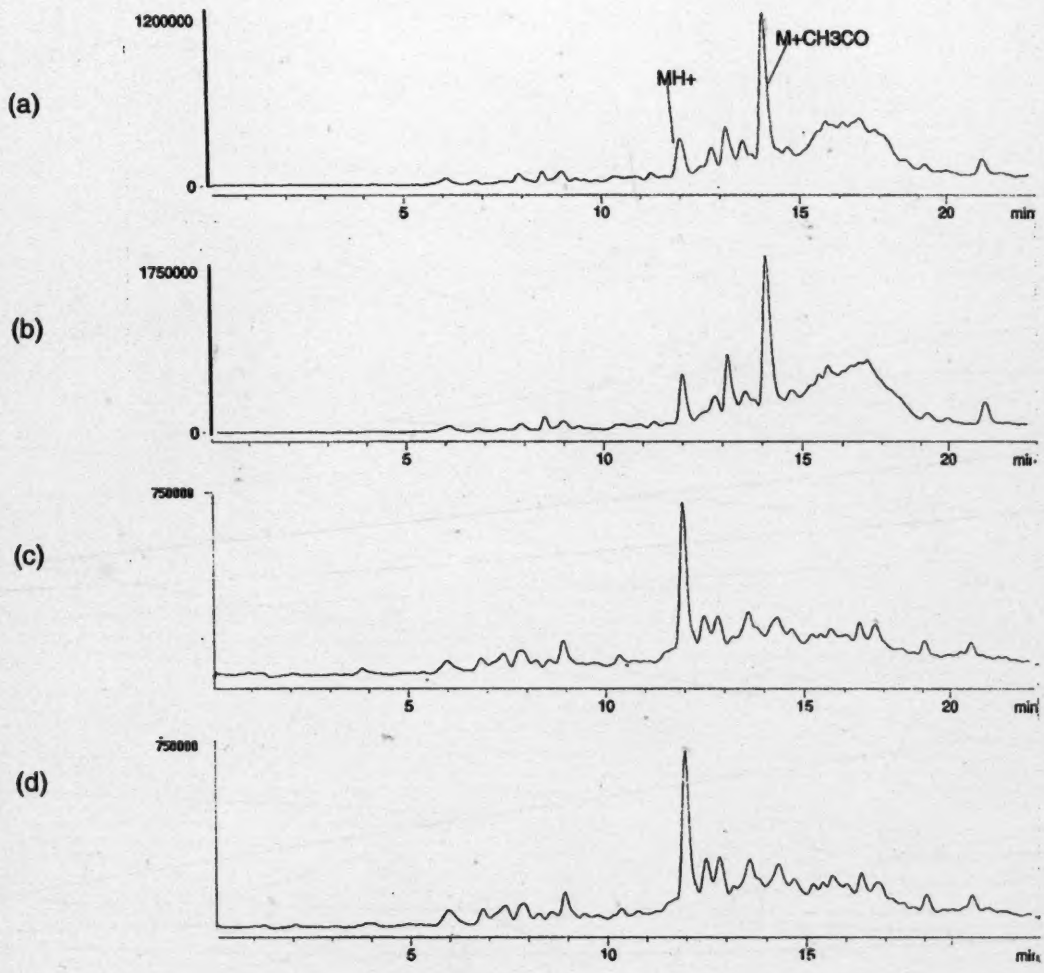


Figure 3. 11: LC-MS of 190 and 193

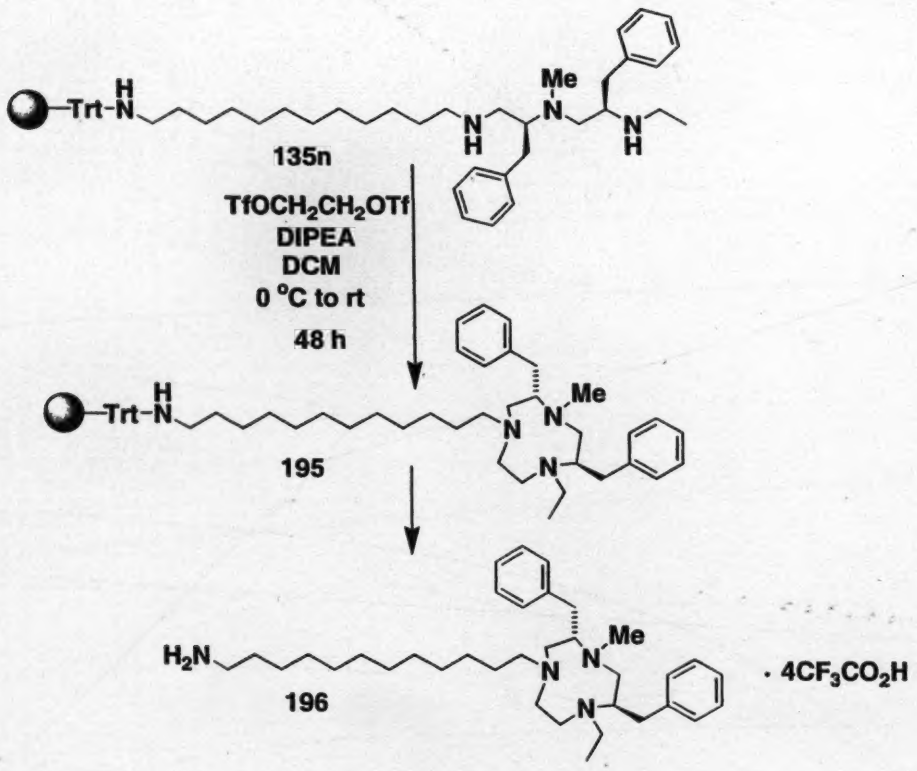
Spectra (a) and (b) represent the total ion current of the crude mixture after acetylation, clearly showing the relative positions of **189** and **194**. Spectra (c) and (d) show the total ion current prior to the acetylation protocol showing the positions of **189** and **190**. Semi-preparative HPLC purification under conditions developed for analytical samples allowed for the isolation of **189** and for its characterization. Typically, the

overall yield of the salt of the triazamacrocycle of interest was found to be low (15-25%), although the yields are based on chlorotrityl polystyrene resin substitution, and also the conservative selection of HPLC fractions.

Epoxidation experiments were also attempted with **189** (as its TFA salt). However, to date, no formation of epoxide has been observed. Perhaps the TFA that is present in the reaction mixture is able to protonate the macrocycle and render it unable to bind manganese, or this particular triazamacrocycle is not a sufficiently good ligand for manganese. In any case, at this point our main concern lies with the development of this methodology, enabling the easy access to the synthesis and purification of the triazamacrocycles, rather than mass production for epoxidation reactions.

3.7: Synthesis of Triazacyclononane 196

The synthesis of **196** was performed as described previously (Scheme 3.25). Two peaks were observed by LC-MS after cleavage of the compound from the solid support, giving **196** and its piperazinium ion side product **197** in a ratio of 2:1. The previously used acetylation protocol was again utilized in an attempt to differentiate between the compounds. Again, it was found that the first peak off the column, with a mass corresponding to the product, remained undifferentiated with a mass of *m/z* 535 and that the second peak disappeared and a peak corresponding to acetylated piperazinium adduct **197** (Figure 3.12) appeared.



Scheme 3. 25

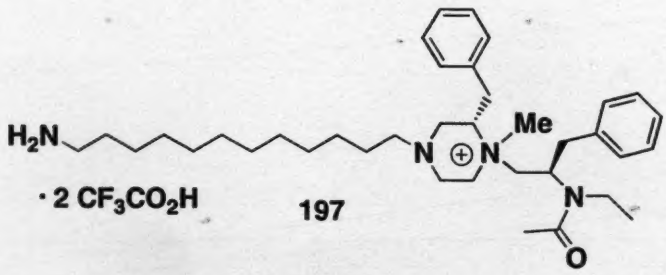


Figure 3. 12: piperazinium ion 197

It was then possible to isolate the desired triazacyclononane **196** by semi-preparative LC-MS and to obtain characterization data. The LC-UV trace after purification is shown below (retention time of 12.590 minutes).

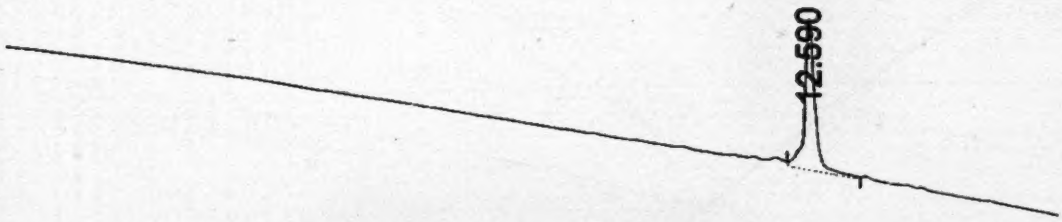


Figure 3. 13: LC-UV-MS of 196

A spectral comparison between the ^{1}H NMR and ^{13}C NMR spectra of compound **196** and triazacyclononane **189** shows some similarities. It was apparent that under the LC conditions used, the compound of interest eluted before the piperazinium side-product **197**.

An epoxidation reaction with this compound has not yet been attempted. It seems very likely that in order for catalytic activity to occur neutralization of the salt would have to be carried out followed by extraction into a suitable organic solvent.

Additional triazacyclononanes were synthesized and purified in a similar fashion, in each case eluting first off the column, using the semi-preparative HPLC column. The compounds were isolated as their *tetrakis*(trifluoroacetate) salts and characterization data was obtained. These other triazacyclononanes, along with the ratios of the desired macrocycle to piperazinium ion, are shown in the figure below (Figure 3.14). Epoxidation reactions have not yet been attempted with these compounds.

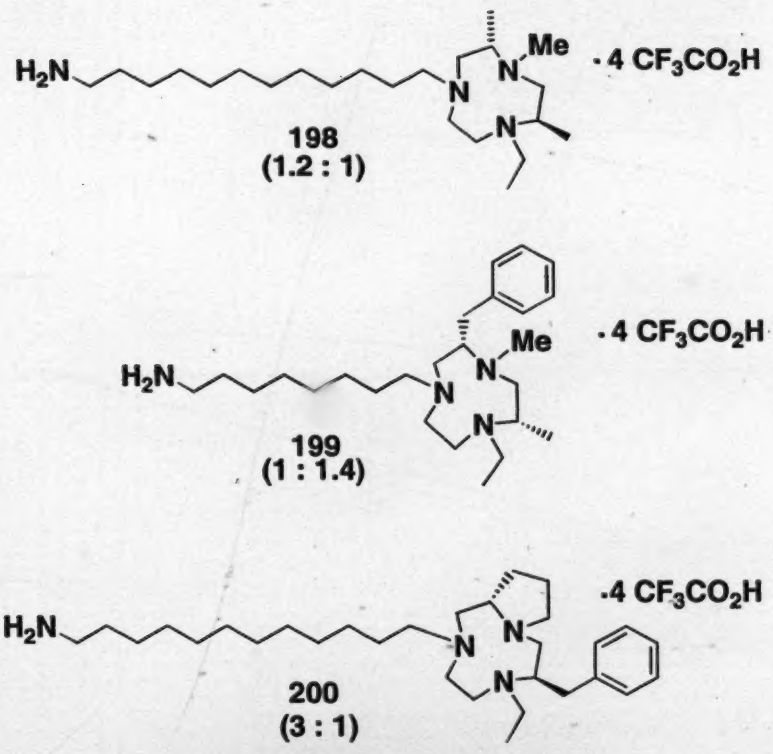
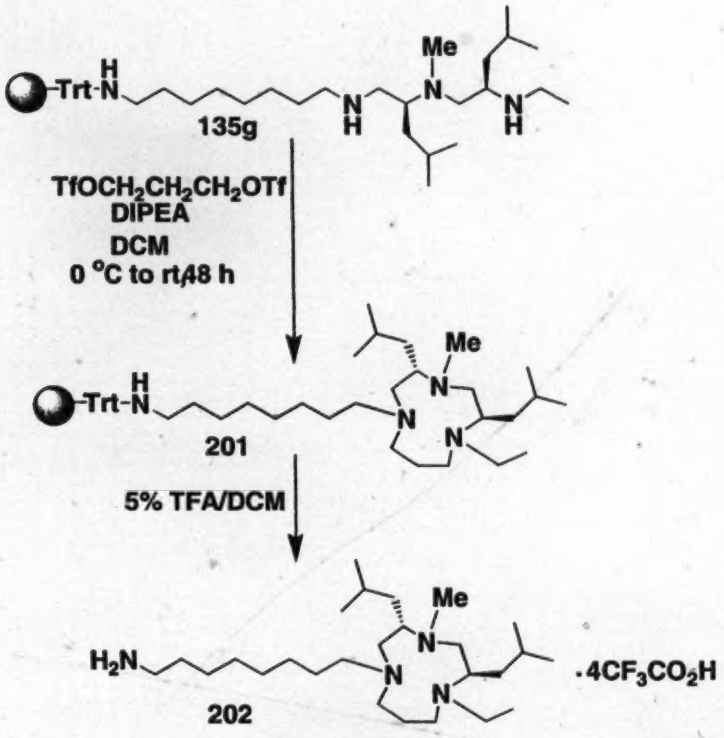


Figure 3. 14: structures and ratios of triazacyclononanes (198, 199, 200) to the corresponding piperazinium ions

3.8: Synthesis Of Triazacyclodecane 202

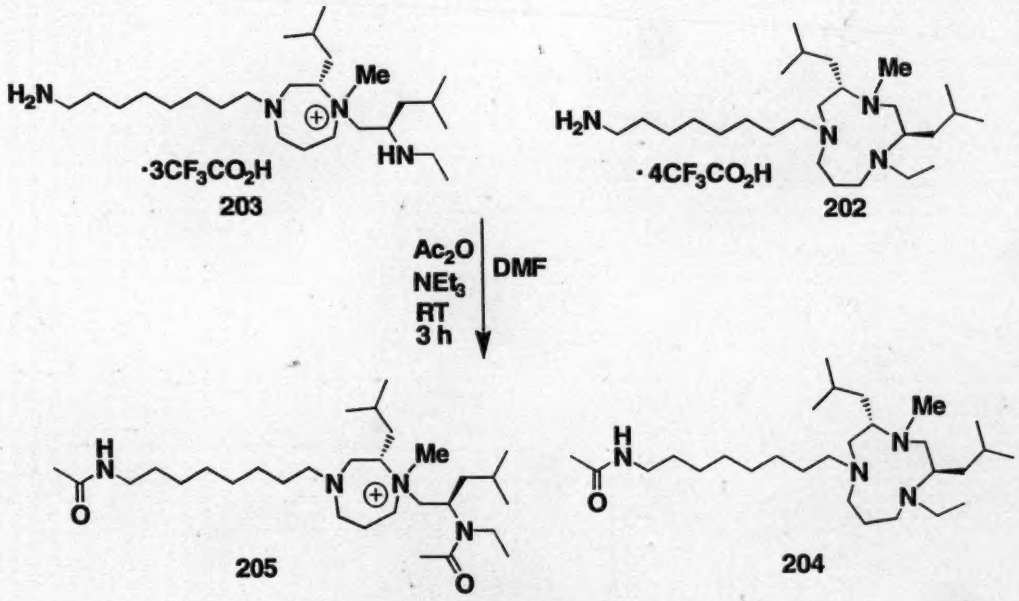
The synthesis of the triazacyclodecane **202** (Scheme 3.26) was analogous to the synthesis of the triazacyclononane molecules. It has been previously shown (Scheme 3.5) that these compounds are readily formed, by reacting the appropriate linear tetramines with the bistriflate of 1,3-propanediol. It was also believed that the formation of a quaternary ammonium side-product in this cyclization reaction would be minimized due to a competition between 7-membered ring and 10-membered ring formation, which would favour the latter. The difference between the rates of formation of 6 versus 9-membered rings is in the order of about 10^5. However, the rates of formation of 7 versus 10-membered rings differ by only about 10^2. We believe that this smaller rate difference, along with the steric considerations of the cyclization reaction, favour the formation of the larger ring system. With this first attempted synthesis, it was determined that two products of identical mass are formed in a ratio of 7:2. The fragmentation

pattern for one of the peaks, the minor one, was that expected for the corresponding quaternary ammonium **203**. In order to determine and confirm that the major product was the desired triazacyclodecane **202**, an acetylation reaction was performed after cleavage of the compounds from the solid support.



Scheme 3. 26

It was gratifying to see that the major product was acetylated only once, giving **204**, and that the minor product was diacetylated to give **205**. This is evident upon examination of the corresponding structures. In this way, it was also demonstrated that the modification of the terminal amino residue could be accomplished selectively if future work required neutralization of its reactivity. In the case of the triazacyclodecane molecules it was determined that the desired compound was the one eluting second from the HPLC column.



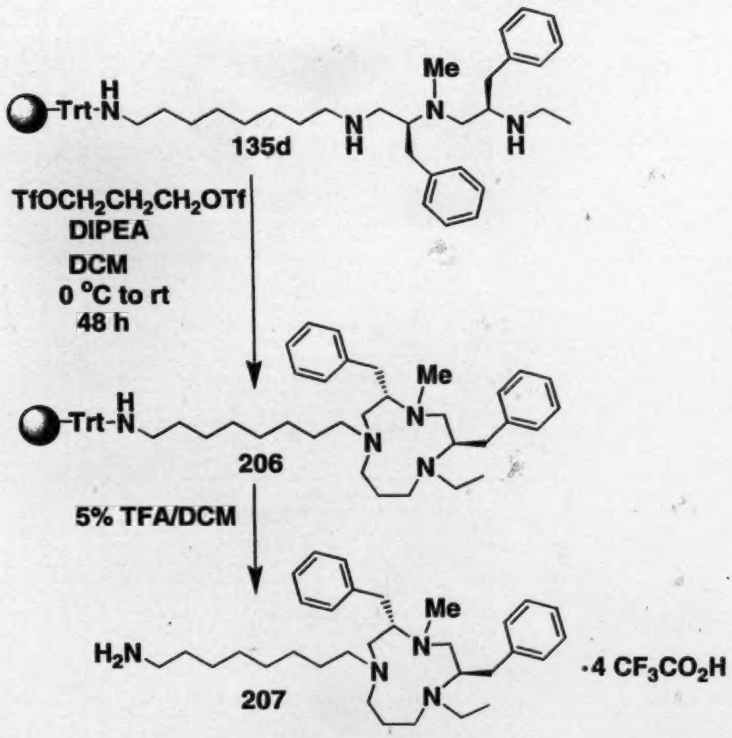
Scheme 3. 27

Purification of compound **204** was performed using semi-preparative HPLC. The spectral data obtained for this compound showed that several regions in the ^{1}H NMR and the ^{13}C NMR spectra bore a similarity to regions of the triazacyclononane compounds.

It should be noted that these compounds are not known to catalyze epoxidation reactions, and that their uses are largely unexplored. In the future, it would be of interest to explore the metal-binding properties of these compounds, obtain crystallographic data for their metal complexes, and explore their chemical reactivity in terms of possible catalytic applications.

3.9: Synthesis Of Triazacyclodecane 207

The synthesis of **207** (Scheme 3.28) was performed as for compound **202**. The analytical LC-MS spectrum showed two peaks corresponding to the desired mass of the compound, in a ratio of > 10:1.



Scheme 3. 28

The first eluted peak showed the fragmentation pattern that was expected for the quaternary ammonium product **208** (Figure 3.15), and a comparison between this HPLC spectrum and the spectrum obtained for **202** showed that the retention times were similar and peak order was identical.

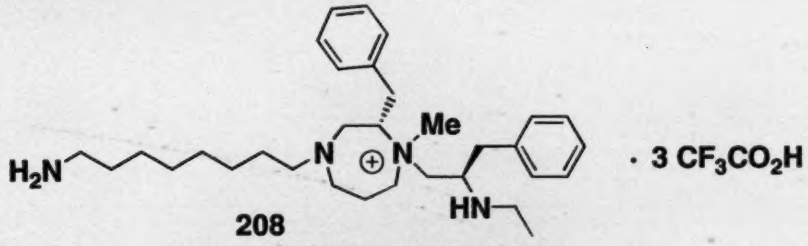
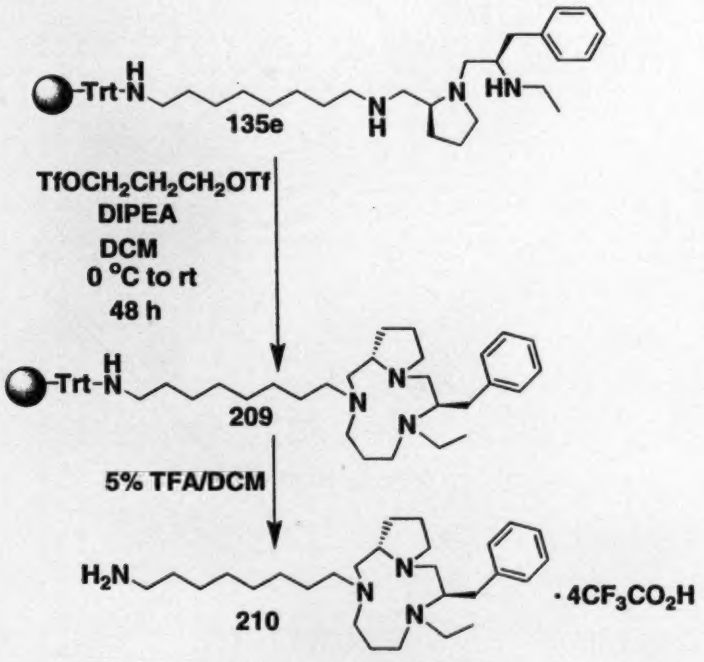


Figure 3. 15: piperazinium ion 208

Semi-preparative purification of this triazacyclodecane **207** was accomplished using the conditions previously developed. Compound **207** was isolated as its *tetrakis*(trifluoroacetate) salt in overall low yield (14%).

3.10: Synthesis Of Triazacyclodecane 210

The synthesis of **210** (Scheme 3.29) proceeded in an analogous fashion to the compounds described previously.



Scheme 3. 29

Semi-preparative purification of **210** was needed after determination that contamination with its quaternary ammonium analogue **211** had occurred (ratio of **210** to quaternary ammonium **211** was 9:1). The compound was isolated as its *tetrakis*(trifluoroacetate) salt and the relevant spectral data was recorded.

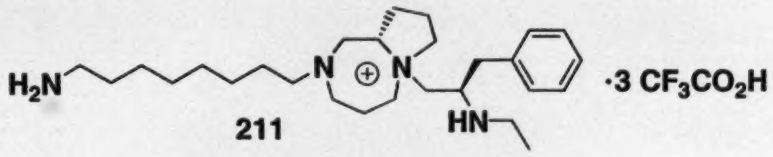
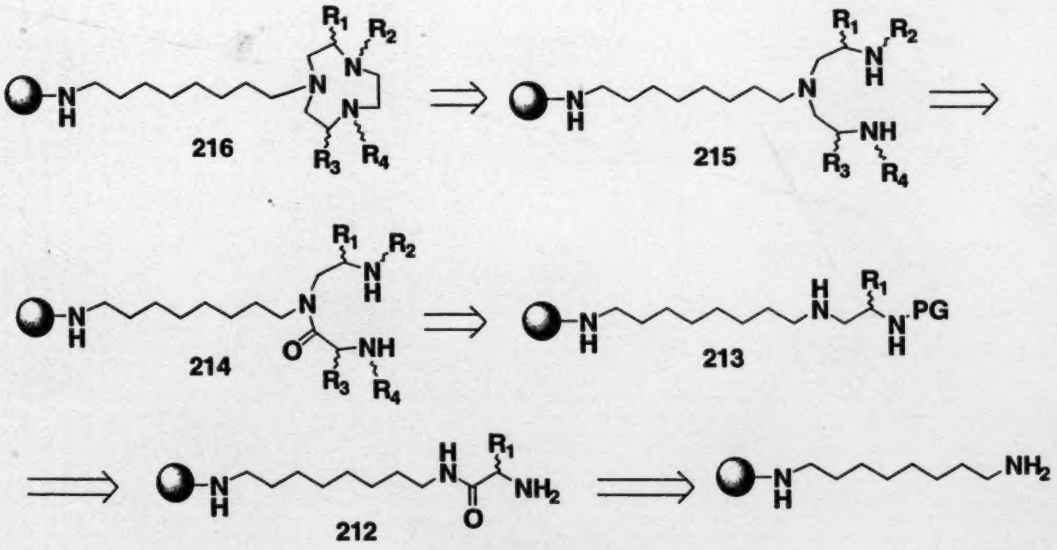


Figure 3. 16: Piperazinium ion 211

3.11: Future Directions

Although it is possible to form the chiral triazacycloalkanes on solid-support, the synthesis suffers from some drawbacks. The major problem with the synthesis is the formation of the piperazinium ions for the triazacyclononane molecules and the corresponding quaternary ammonium ion for the triazacyclodecane molecules. Our offered explanation for this is that there is a competitive cyclization that occurs upon the second nucleophilic attack on the bistriflate (Scheme 3.20). One other drawback is that, as a result of the above side-reaction, a semi-preparative purification of the products is necessary which is both time-consuming and inconvenient. An alternate route is therefore highly desirable in order to facilitate the synthesis of eventual ligand libraries.

Prior to the publication by Kim on the synthesis of peraza-macrocycles using chiral aziridines,[39] work had begun on the synthesis of 'back-bone' chiral triazacycloalkanes utilizing a similar strategy. The goal of this project was to synthesize a branched oligoamine using a selective primary amine protection strategy and two amide reduction protocols developed in our laboratory[12], all with 1,8-diaminooctanoyl as the linker. The branched oligoamine could then be cyclized using a Richman-Atkins strategy employing Cs_2CO_3 as the base and either 1,2-dibromoethane or the bistriflate of ethylene glycol as the electrophile. A retrosynthetic scheme is presented below (Scheme 3.30).



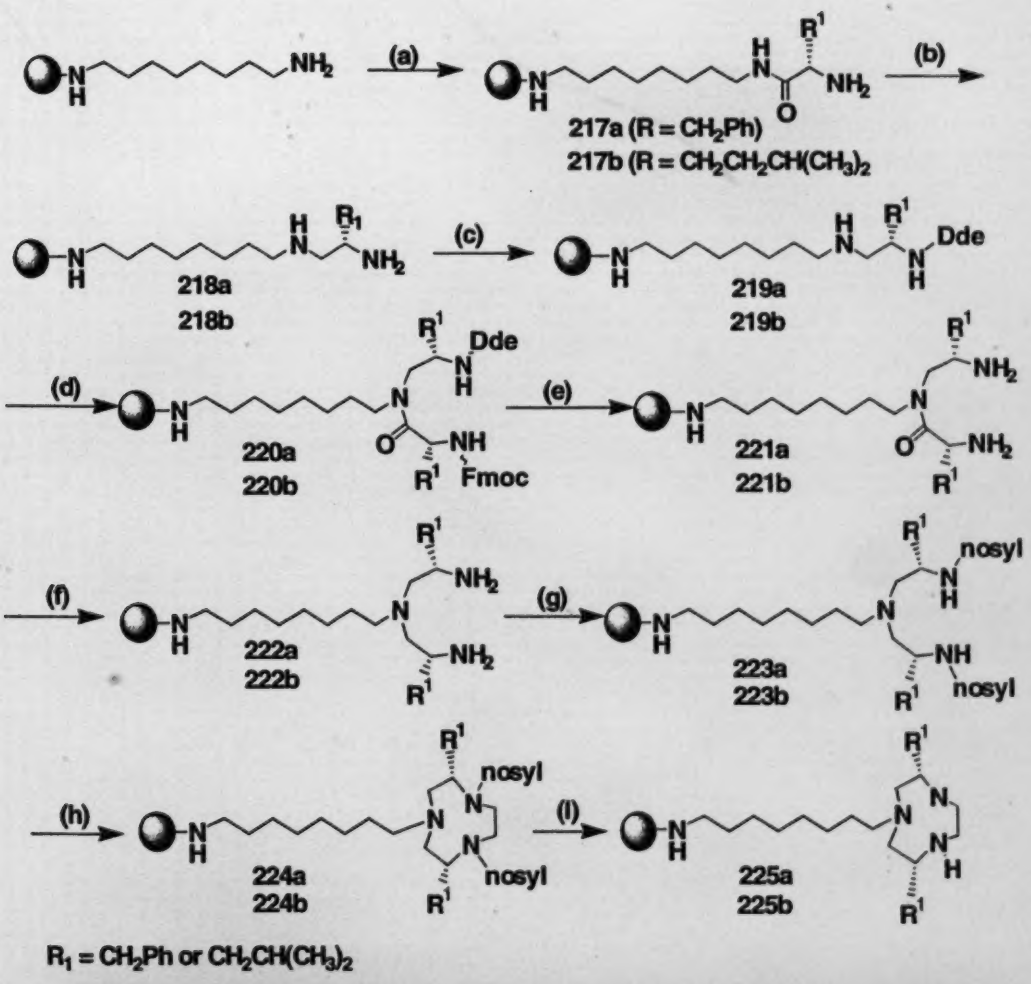
Scheme 3. 30

There would appear to be a few potential difficulties with this approach. Firstly, in order to form a branch on the amine chain attached to the solid-support, the primary amine functional group would have to be selectively protected in the presence of a secondary amine to give **213**. This problem could be overcome by the use of 2-acetyldimedone (Dde-OH) as the primary amine protecting group, which is known to selectively protect primary amines in the presence of secondary amines.[49] Secondly, there is the need for two consecutive reduction protocols that would both have to proceed cleanly in order to form the desired precursor **215** in high yield and purity. This problem could be overcome by testing the applicability of the reduction protocols developed both in our laboratories[12,63,70] and those of other research groups.[11] Thirdly, is the use of 2-nitrobenzenesulfonylchloride (nosyl-Cl) as a nitrogen activating agent, allowing **215** to be cyclized under Richman-Atkins conditions.[71,72] The use of the nosyl group in a Richman-Atkins macrocyclization has been demonstrated in a recent solution-phase synthesis.[73] The advantage of this group is that its cleavage can be affected under mild conditions using a thiol.

Synthesis of triazacyclononane **225a/b** began with selecting Fmoc-protected L-phenylalanine and Fmoc-protected L-leucine as the amino acid residues to be

incorporated into two model trizacyclononane molecules. Coupling of the first amino acid residue (R = CH_2Ph or $CH_2CH(CH_3)_2$) using standard coupling techniques yielded amide **217a** or **217b** (Scheme 3.31). Deprotection of the Fmoc group was followed by reduction with a 1 M BH_3/THF solution, giving the desired amine **218a/b** in good yield and purity. As expected, selective protection of the primary amine was accomplished using 2-acetyldimedone as the protecting group which was confirmed by cleavage of a small portion of the compound from the solid-support followed by analysis of the resultant trifluoroacetate salt of **218a/b** by ES-MS. The result was also confirmed qualitatively by a ninhydrin assay.[51]

The coupling of a second amino acid residue (Fmoc-L-Phe-OH or Fmoc-L-Leu-OH) was carried out using HATU **89** as the coupling reagent in accordance with the literature[57] providing the di-protected amide **220a/b**. Cleavage of the protecting groups followed, giving amide **221a/b** that was confirmed by ES-MS of a cleaved sample and by ninhydrin assay.[51]



Reaction conditions: (a) (i) 4 equiv. HOBt, 4 equiv. HBTU, 4 equiv. Fmoc-L-Phe-OH, 8 equiv. DIPEA, DMF (ii) 20% piperidine/DMF (b) (i) 40 equiv. BH_3/THF, 65 °C 24 h (ii) I_2/ AcOH/ DIPEA/ THF (c) 2-acetyldimedone/DMF (d) 4 equiv. HATU, 4 equiv. Fmoc-L-Phe-OH, 8 equiv. DIPEA (e) (i) 2% NH_2NH_2/ DMF (ii) 20% piperidine/DMF (f) (i) 12 equiv. $B(OH)_3$, 12 equiv. $B(OMe)_3$, 40 equiv. BH_3/THF, 65°C, 24 h (ii) piperidine, 65 °C, 24 h (g) 2-nitrobenzenesulfonyl chloride, NEt_3, DCM (h) Cs_2CO_3, $TsOCH_2CH_2OTs$, DMF (i) PhSH, K_2CO_3, DMF

Scheme 3. 31

Reduction of **221a/b** was accomplished using both our own borane reduction protocol and Houghten's protocol[11] comparably affording **222a/b** in good yield and purity, although the latter reduction protocol gave slightly better results. The primary amine groups on this oligoamine were then protected with 2-nitrobenzenesulfonyl chloride[73] giving the di-protected oligoamine **223a/b** which was confirmed by LC-MS

(> 90% purity) carried out on a cleaved sample. The cyclization protocol was attempted using Cs_2CO_3 in DMF, and the bistosylate of ethylene glycol. However, this reaction has proven difficult to date with only minimal product formation observed.

In the future it will be necessary to elucidate the right conditions for the cyclization of **223a/b** to yield the desired protected triazacyclononane **224a/b**. It would appear possible that if a competitive cyclization does indeed occur with this method the branching tertiary nitrogen atom can be left as the amide and the cyclization protocol can be attempted on amide **221a/b** after appropriate activation. This can then be followed by deprotection and final reduction of the amide-containing macrocycle.

When this cyclization is accomplished it will be necessary to deprotect **224a/b** and then perhaps further functionalize the resultant secondary amines of **225a/b**. This method appears to hold a great deal of promise for the formation of the desired chiral triazacyclononanes, especially in light of what has been so elegantly demonstrated by Kim in his recent report.[38]

3.12: Summary and Conclusions

The importance of polyamines in nature has led organic chemists to develop synthetic methods toward their synthesis. Those methods that rely on a solution phase approach have traditionally been used in order to access these structures. However, these methods suffer from a few shortcomings. The synthesis of the polyamines in solution relies heavily on protection/deprotection methods, as well as the chromatographic separation of the often complex mixtures that are obtained. This complication has forced chemists to seek other methods for their synthesis.

The solid-phase approach offers advantages for the synthesis of organic compounds. In this approach one is able to immobilize a substrate by anchoring it to an appropriate polymer matrix. This allows for the use of an excess of reagents, which drives the reaction to completion. Another benefit is that the excess reagents can be removed from the reaction by filtration and utilizing the different swelling properties of the resin in various solvents through extensive washings. Oftentimes these conditions lead to an increased yield of the desired product, especially if the transformation can be highly controlled.

The solid-phase approach also has some disadvantages. The primary disadvantage is that if any reaction engenders side products, these undesired compounds cannot be removed from the resin until the desired mixture is cleaved from the support. Therefore in a multi-step synthesis each undesired transformation leads to an accumulation of impurities. Another disadvantage with the solid-supported approach is that reactions must be run under relatively mild conditions for a variety of polymers so that the substrate remains bound to the bead until its cleavage is warranted.

In this project tritylchloride polystyrene was used as the solid-support because of the ease of handling of this polymer and the previous work done in our laboratories with this support. Several spacers were utilized for the preparation of the peptides; 1,3-diaminopropane, 1,8-diaminooctane, 1,12-diaminododecane, and 4-aminomethylpiperidine. These spacers allowed for the direct attachment of two Fmoc-protected α-amino acids through the use of standard coupling reagents such as HOBt, HBTU, and HATU.

A variety of tripeptides were constructed of two general types. The first type of tripeptide coupled two α-amino acids to form oligo(*sec*-amides). The second type of tripeptide coupled an *N*-methylated-α-amino acid with a non-methylated-α-amino acid through the use of the HATU coupling reagent, providing a tertiary amide residue in the resultant tripeptide. In general, these peptides were synthesized in high yield and purity.

The corresponding linear oligoamines were then synthesized from the tripeptides. The mild protocol developed in our laboratories was used to obtain these products. This protocol calls for the use of a borane-tetrahydrofuran reduction followed by a mild, buffered, iodine-promoted cleavage of the intermediate borane-amine adducts. This method provided the corresponding oligo(*sec*-amines) in good yield and purity. The product of the reduction and work-up for the tripeptide containing a tertiary amide residue was determined to be a bicyclic borane-amine adduct that proved to be quite robust. In order to obtain the free oligoamine containing a tertiary amine residue the oxidative work-up had to be modified to include a round of basic ethylene glycol treatment.

The demand for tertiary oligoamines prompted us to investigate their synthesis. In principle it could be possible to obtain these tertiary amines by coupling secondary

amines with an appropriate amino acid. However, it is known that these coupling reactions are sluggish. Instead, we decided to attempt to directly access them through direct modification of the olig(*sec*-amines). It was found that addition of an aldehyde (other than benzaldehyde) to the resin directly after it has been subjected to borane reduction, in the presence of an external hydride source such as sodium triacetoxyborohydride, led to the formation of the oligo(*tert*-amines) in good yield and purity.

Manganese complexes of triazacyclononane compounds have been shown to catalyze the epoxidation of olefins and the development of chiral ligands for these reactions is a high priority for several research groups around the worid. The oligoamines containing a tertiary amine residue were used as precursors to the triazacycloalkane molecules. The triazacycloalkane molecules were obtained through a bistriflate promoted cyclization of the linear tetramine. Unfortunately the synthesis suffers from a competitive reaction in which a piperazinium ion (for the triazacyclononane molecules) and the corresponding quaternary ammonium ion (for the triazacyclodecane molecules) are formed in significant amounts. Nevertheless, this methodology to access the triazacycloalkane molecules constitutes a step forward in the chemistry of these molecules because the majority of other methods are limited to the modification of the triazacycloalkane skeleton by altering the nitrogen atoms of the macrocycle. Our method is one of the only ways to access chiral triazacycloalkanes that place the chiral substituents on the carbon framework of the macrocycle.

The purification of these compounds was achieved through semi-preparative HPLC and the compounds were obtained in an overall low yield (14-25%) as a result of the quaternary ammonium impurity and the difficult purification procedure. Some of these compounds were tested for their ability to epoxidize styrene with promising results. However, to date, no enantiomeric excess has been seen for the product of styrene oxide, perhaps as a result of a radical mechanistic pathway for aromatic alkenes.

An alternative, and perhaps better route to the triazacycloalkane molecules using a Richman-Atkins cyclization has been preliminarily investigated. Prior to the recent synthesis reported by Kim[39] work began on constructing a branched oligoamine molecule. The branched amine could be formed by a peptide coupling/reduction/peptide

coupling/reduction sequence. Attempts at forming the macrocycle show promise. With this methodology it is possible to forego the second reduction step until after the cyclization protocol. These proposed modification will be tested in the Hall laboratory in the near future.

4. Experimental Section

4.1: General

All Fmoc-amino acids and reagents employed are commercially available and were used without purification. All resins used were purchased from Rapp-Polymere (Tübingen, Germany) or NovaBiochem (San Diego, California). The loading value stated by the supplier was used in all cases. Solid phase reactions performed at room temperature were performed in polypropylene vessels (PP) or in round-bottom flasks. THF was dried and distilled over sodium/benzophenone ketyl. Anhydrous DMF was obtained commercially and stored at 4 °C to reduce decomposition to dimethylamine and carbon dioxide. Solutions of 1 M BH_3·THF were obtained from Aldrich in 100 ml sizes and were stored at 4 °C. ^1H NMR spectra were recorded at either 300 MHz, 400 MHz or 500 MHz in CD_3OD, all ^{13}C NMR (BB, APT or DEPT), were recorded at 75.5, 100, or 125 MHz in CD_3OD (chemical shifts for both the proton and carbon NMR are expressed in parts per million and were referenced against residual CH_2DOD). Analytical HPLC, using either UV (210 and 250 nm) or ES-MS detection (atmospheric pressure ionization, quadrupole detector in positive mode), was performed on a Zorbax SB-C8 (4.6 x 50 mm, 3.5 μm) column using a gradient method of 2% acetonitrile (0.1% TFA) and 98% water (0.1% TFA) to 50% acetonitrile over 12 min and maintained for a further 8 min at a flow rate of 0.7 ml/min. Semi-preparative HPLC, using UV detection (210 or 250 nm), was performed on a Zorbax Rx-C8 semi-preparative column (9.4 x 250 mm, 5 μm) using a gradient method of 2% acetonitrile (0.1% TFA) and 98% water (0.1% TFA) to 50% acetonitrile (0.1% TFA) and 50% water (0.1% TFA) over 12 min. and maintained at this concentration for a further 8 min. at a flow rate of 0.7 ml/min. Chiral HPLC, using UV detection (250 nm) was performed on a CHIRALCEL OD column (0.46 cm I.D. × 25 cm, 0.25 ml/min flow rate) using 30% isopropanol/water as the eluent. Evidence of TFA salt formation was not quantified but was qualitatively observed in the ^{13}C NMR spectra of the products. An excess of TFA was used in the cleavage reactions of the compounds from the trityl polystyrene resin and an assumption was made of compelete protonation of the products to form the corresponding TFA salts. Determination of the number of

protonated amine sites by TFA could be performed using ^{19}F NMR spectroscopy, but this was not done in this work.

4.1.1: General Procedure For The Preparation Of Tripeptides:

In a polypropylene vessel, the diaminotrityl polystyrene resin was swollen with 3 × CH_2Cl_2 and 3 × DMF washings. The bottom of the PP vessel was then capped. To the resin was then added a small amount of DMF, enough to just cover the top of the resin. To the vessel was added 8 equivalents of DIPEA (based on resin loading) that was followed by 1 minute of mixing on a vortexer. Four equivalents of the Fmoc-protected amino acid, HOBt, and HBTU (based on resin loading) were dissolved in DMF in separate flasks and added to the PP vessel sequentially. The vessel was capped and sealed and placed on an agitator for 3 hours at room temperature. The resultant suspension was drained and washed successively with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin assay was negative.[51] The Fmoc protecting group was then cleaved with a 20% piperidine/DMF solution for 45 minutes after which a bromophenol blue assay was positive. The resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2, and finally 3 × DMF. The second peptide coupling was analogous to the first. To the resin, suspended in DMF in the PP vessel, was added 8 equivalents of DIPEA, followed by 1 minute of vortexing. To this suspension was then added 4 equivalents of the α-amino acid, 4 equivalents of HBTU, and 4 equivalents of HOBt. This PP vessel was capped and sealed and agitated for 3 hours at room temperature. The suspension was drained and the resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. The Fmoc-protecting group was removed with a 20% piperidine/DMF solution and the resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin assay was positive[51]. The resin was swollen with 3 × DMF, and suspended in DMF, and to this was added 0.4 ml/g resin triethyl amine and 1 ml/g resin of acetic anhydride. The suspension was shaken for 2 hours at which point the resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin assay was negative.[51] The resin was then dried *in vacuo* for >12h

4.1.2: General Procedure For The Preparation Of *N*-Methylated Resin-Bound Tripeptides

In a polypropylene vessel, the diaminotrityl polystyrene resin was swollen with 3 × CH_2Cl_2 and 3 × DMF washings. The bottom of the PP vessel was then capped. To the resin was then added a small amount of DMF, enough to just cover the top of the resin. To the vessel was added 8 equivalents of DIPEA (based on resin loading) that was followed by 1 minute of mixing on a vortexer. Four equivalents of the Fmoc-protected *N*-methylated amino acid, HOBt, and HBTU (based on resin loading) were dissolved in DMF in separate flasks and added to the PP vessel sequentially. The vessel was capped and sealed and placed on an agitator for 3 hours at room temperature. The resultant suspension was drained and washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2 . A ninhydrin assay was negative.[51] The Fmoc protecting group was then cleaved with a 20% piperidine/DMF solution for 45 minutes after which a bromophenol blue assay was positive. The resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2, and finally 3 × DMF. The second peptide coupling was analogous to the first except that the coupling reagent was HATU. To the resin in the PP vessel covered with DMF was added 8 equivalents of DIPEA, followed by 1 minute of vortexing. To this suspension was then added 4 equivalents of the α-amino acid and 4 equivalents of HATU. This PP vessel was capped and sealed and agitated for 3 hours at room temperature. The suspension was drained and the resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. The Fmoc-protecting group was removed with a 20% piperidine/DMF solution and the resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin assay was positive.[51] The resin was swollen with 3 × DMF, and suspended in DMF, and to this was added 0.4 ml/g resin triethyl amine and 1 ml/g resin of acetic anhydride. The suspension was shaken for 2 hours at which point the resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin assay was negative.[51] The resin was then dried *in vacuo* for >12 h.

4.1.3: General Procedure For The Reduction Of Tripeptides

The tripeptide containing resin was placed in a round-bottom flask that was fitted with a condenser and a nitrogen inlet. The flask was evacuated and filled with nitrogen. To this was added enough dry THF to just suspend the resin. Then 40 equivalents of 1 M BH_3/THF (based on resin loading) were added via syringe. The reaction mixture was heated to 65 °C with stirring and the suspension was maintained at a gentle reflux for 24 h under nitrogen. The suspension was cooled and poured into the appropriate PP vessel and drained. The resin was washed with 3 × THF and re-suspended in a small amount of THF. To this was added 2 ml/g resin DIPEA followed by 4 ml/g resin acetic acid and the suspension was well mixed. This was followed by the addition of 20 equivalents of I_2 as a concentrated THF solution. The dark suspension was shaken vigorously on a shaker for 3.5-4 hours and then drained. The resin was washed with 3 × THF, 3 × Et_3N/DMF (1:3), 3 × MeOH, and finally 3 × CH_2Cl_2. The resulting resin was then dried *in vacuo* for > 12 h.

4.1.4: General Procedure For The Reduction Of *N*-methylated Tripeptides

The *N*-Methylated tripeptide containing resin was placed in a round-bottom flask that was fitted with a condenser and a nitrogen inlet. The flask was evacuated and filled with nitrogen. To this was added enough dry THF to just suspend the resin. Then 40 equivalents of 1 M BH_3/THF (based on resin loading) were added via syringe. The reaction mixture was heated to 65 °C with stirring and the suspension was maintained at reflux for 5 days to ensure complete reduction. The suspension was cooled and poured into the appropriate PP vessel and drained. The resin was washed with 3 × THF and re-suspended in a small amount of THF. To this was added 2 ml/g resin DIPEA followed by 4 ml/g resin acetic acid and the suspension was well mixed. This was followed by the addition of 20 equivalents of I_2 as a concentrated THF solution. The dark suspension was shaken vigorously on a shaker for 3.5-4 hours and then drained. The resin was washed with 3 × THF, 3 × Et_3N/DMF (1:3), 3 × MeOH, 3 × CH_2Cl_2, and 3 × THF. This was followed by re-suspending the resin in THF and adding 2 ml/g resin DIPEA and 4 ml/g

resin ethylene glycol and the resulting suspension was placed on a shaker overnight. The resin was then washed with 3 × THF, 3 × MeOH, and 3 × CH_2Cl_2. The resin was then dried *in vacuo* for >12 h.

4.1.5: General Procedure For The Preparation Of The Azacycloalkanes

Resin-bound polyamine (**135 a-n, 105**), in a round-bottom flask equipped with a stir bar, was suspended in approximately 5 ml of CH_2Cl_2. To the suspension was added 8.5 equiv. of *N,N*-Diisopropylethylamine and the flask was fitted with a pressure-equalizing dropping funnel before being cooled to 0 °C in an ice-water bath. The dropping funnel was charged with 10-15 equiv. of the freshly prepared bis-triflate as a dilute solution in CH_2Cl_2 (typically 0.14-0.17M). The bis-triflate solution was then added to the resin, maintained at 0 °C, over a period of 6 h (no special precautions were taken to exclude air), at which point the suspension was allowed to warm up to room temperature. The resin was stirred in the solution for a further 42 h at which point it was filtered through a polypropylene vessel and washed first with 3 × 5 ml CH_2Cl_2, then with 3 × 5 ml MeOH, and finally with 3 × 5 ml CH_2Cl_2. The resin was subsequently dried under vacuum for > 12 h and portions of the resin were cleaved by a 5% TFA/CH_2Cl_2 solution, that was evaporated and dried *in vacuo* overnight (> 12 h) for analysis by analytical HPLC and purification by semi-preparative HPLC.

4.1.6: General Procedure For The Catalytic Epoxidation Of Styrene

4.1.6.1: Resin Bound Ligand As Catalyst

To 40 μmol of resin bound ligand, in a small round bottom flask containing 1 ml of DMF and a stir bar, was added 25 μmol of a 0.150 M $MnSO_4 \cdot 2H_2O$ solution (166.7 μl) *via* analytical pipet. To this suspension was also added 77μl of styrene (0.67 mmol, 0.909 gml^{-1}). The suspension was stirred for 10 minutes at which point a solution of Na-oxalate (0.23 M, 1 ml) and H_2O_2 (6.7 mmol, 0.21 ml) was added in 50 μl portions every 30 minutes over 10 hours. The resulting suspension was stirred overnight. The suspension was filtered and the filtrate was diluted to 10 ml with water. The resulting

solution was transferred to a separatory funnel and extracted with 3 × 10 ml pentane. The combined pentane washes were dried with $MgSO_4$ (anhydrous), filtered, and concentrated on the rotovap. The pentane solution was not allowed to totally evaporate to dryness. Determinations of epoxide yield were made using ^1H NMR spectroscopy and the relative ratios of styrene to styrene oxide were made on the basis of integrated peak area.

4.1.6.2: Solution-Phase Ligand As Catalyst

The solution phase synthesis was as described in section 4.1.6.1 except that the filtration step was omitted because the ligand was in solution.

4.1.7: General Procedure For The Cleavage Of Trityl Polystyrene Resisns

A 50 mg sample of the resin containing the desired compound is placed inside a small round bottom flask containing a stir bar and then suspended in 2 ml of CH_2Cl_2. To the stirred suspension 100 µL of trifluoroacetic acid is added in one portion via glass syringe. The resulting red suspension is stirred for an additional 2 h at room temperature taking no special precautions to exclude air. The resin is then filtered through a cotton plug in a glass pipette. The resin on top of the plug is then rinsed with enough CH_2Cl_2 to remove the red colour, and then finally with 3 ml of MeOH. The solution is then evaporated and the resultant oil dried *in vacuo* overnight (> 12 h).

4.1.8: General Method For The Determination Of Resin Loading

Theoretical Substitution:

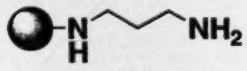
$$S_{(th)} = \frac{S_{(s)}}{1 + \frac{\{ S_{(s)} \times Wt_{(add)} \}}{1000}}$$

$S_{(s)}$ = starting substitution in mmol/g

$Wt_{(add)}$ = g/mol added to resin

4.2: Linker Synthesis

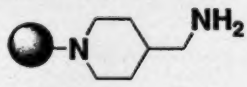
4.2.1: Synthesis Of 1,3-diaminopropanylpolystyrene 106:



106

In a round-bottom flask, 1,3-diaminopropane (100 equiv. based on resin loading) was dissolved in CH_2Cl_2. To this was added in small portions over 1 h tritylchloride polystyrene resin. The resulting suspension was transferred to a PP vessel and washed with 3 × CH_2Cl_2 , 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin assay was positive.[51]

4.2.2: Synthesis Of 4-aminomethylpiperidine polystyrene 79

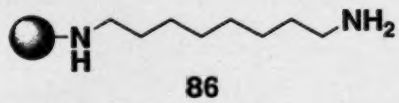


79

To 1.00 g (8.76 mmol) of 4-aminomethylpiperidine in DMF, in a round-bottom flask, was added 1.1 equivalents of 2-acetyldimedone (1.62 g, 8.90 mmol) in 15 ml of DMF. The resulting red solution was stirred under nitrogen for 2 h at which point 3.0 ml of triethylamine were added. The solution was allowed to stir overnight. The DMF was evaporated leaving a yellow solid that was confirmed to be the protected amine by ES-MS (MH^+ = 279 *m/z*). Four equivalents of the protected diamine dissolved in DMF were then added to tritylchloride polystyrene resin in a PP vessel suspended in DMF. The suspension was shaken overnight on the shaker and the resin was then washed with 3 × DMF, 3 × MeOH, 3 × CH_2Cl_2. The resin was then suspended in a 1:1 mixture of CH_2Cl_2/ MeOH and was further mixed for 3 h. The resin was washed with 3 × MeOH and 3 × CH_2Cl_2. A ninhydrin assay was negative at this point.[51] The resin was swollen in DMF

and the protecting group was cleaved using a 2% hydrazine/DMF solution. A ninhydrin colorometric assay was positive.[51]

4.2.3: Synthesis Of 1,8-diaminooctanylpolystyrene 86

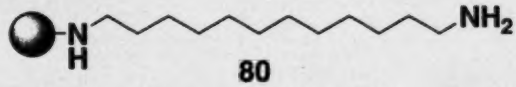


86

In a round-bottom flask, 1,8-diaminooctane (50 equivalents based on resin loading) was dissolved in DMF at 50° C. To this was added in small portions over 1 h tritylchloride polystyrene resin. The resulting suspension was transferred to a PP vessel and washed with 3 × CH_2Cl_2, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin assay was positive.[51] A small portion of this resin was transferred to a small PP vessel and swollen in DMF. This was then treated with 1 ml/g resin acetic anhydride and 0.4 ml/g resin triethylamine for 2 h. Cleavage of this sample with 5% TFA/CH_2Cl_2 afforded the acetylated diamine **89** along with non-acetylated diamine. Analytical LC-MS showed the resin to be > 95% cross-link free.

LC-ES-MS: Rt = 7.840 min. acetylated diamine; 7.314 min. non-acetylated diamine.

4.2.4: Synthesis Of 1,12-diaminododecylpolystyrene 80



80

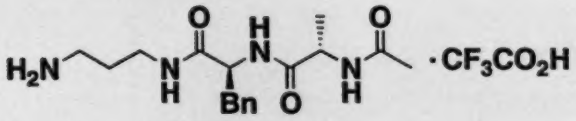
In a round-bottom flask, 1,12-diaminododecane (50 equivalents based on resin loading) was dissolved in DMF at 50° C. To this was added in small portions over 1 h tritylchloride polystyrene resin. The resulting suspension was transferred to a PP vessel and washed with 3 × CH_2Cl_2, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin assay was positive.[51] A small portion of this resin was transferred to a small PP vessel and swollen in DMF. This was then treated with 1 ml/g resin acetic anhydride and 0.4 ml/g resin triethylamine for 2 h. Cleavage of this sample with 5% TFA/CH_2Cl_2 afforded the

acetylated diamine **83** along with non-acetylated diamine. Analytical LC-MS showed the resin to be > 90% cross-link free.

LC-ES-MS: Rt = 12.357 min. acetylated diamine; 9.771 min. non-acetylated diamine.

4.3: Synthesis Of Tripeptides

4.3.1: Synthesis Of Tripeptide 109a



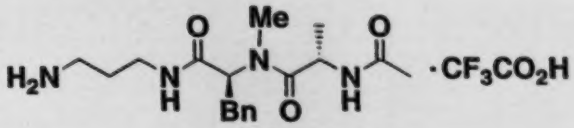
109a

Tripeptide **109a** was prepared according to general procedure 4.1.1. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **109a** as its trifluoroacetate salt in 95% yield.

^{1}H NMR (300 MHz, CD_3OD): δ: 7.35 - 7.18 (m, 5H), 4.46 (dd, J_1 = 8.7 Hz, J_2 = 6.3 Hz, 1H), 4.14 (quart. J =7.2 Hz, 1H), 3.24 (t, J = 8.4 Hz, 2H), 3.16 (dd, J_1 =13.8 Hz, J_2 = 6.3 Hz, 1H), 3.00 (dd, J_1 =13.8 Hz, J_2 =8.7 Hz, 1H), 2.83 (dt, $J1$ = 3.3 Hz, $J2$ = 7.2 Hz, 2H), 1.96 (s, 3H), 1.77 (quint., J = 6.8 Hz, 2H), 1.22 (d, J = 7.2 Hz, 3H).

^{13}C NMR (APT, 75.5 MHz, CD_3OD): δ: 175.3 (C), 174.1 (C), 173.9 (C), 138.4 (C), 130.2 (CH), 129.5 (CH), 127.9 (CH), 56.3 (CH), 51.2 (CH), 38.1 (CH_2), 38.0 (CH_2), 36.9 (CH_2), 28.5 (CH_2), 22.5 (CH_3), 17.3 (CH_3). ES-MS m/z $(M + H)^+$ = 335.4

4.3.2: Synthesis Of Tripeptide 109b



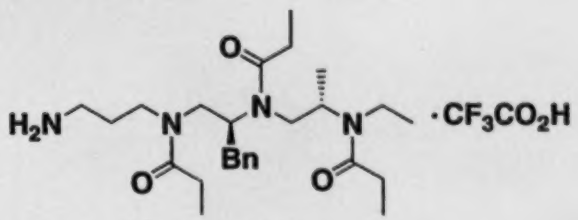
109 b

Tripeptide **109b** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **109b** as its trifluoroacetate salt in 88% yield.

^{1}H NMR (CD_3OD, 300 MHz): δ (mixture of rotamers): 7.40-7.20 (m, 2 × 5H), 5.05 (dd, 1H, J_1 = 2.5 Hz, J_2= 10.6 Hz), 4.60-4.45 (m, 2 × 1H), 4.40 (q, 1H. J = 6.2 Hz), 2.85 (s, 3H), 2.84 (s, 3H), 3.42-2.80 (m 2 × 4H), 1.87 (s, 3H), 1.85 (s, 3H), 1.77 (m, 2 × 2H), 1.18 (d, 2H, J = 5.9 Hz), 0.36 (d, 2H, J = 6.0 Hz).

ES-MS m/z $(M + H)^+$ = 349

4.3.3: Synthesis Of Triamide 111



111

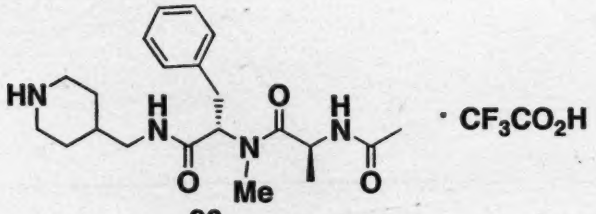
Triamide **109a** containing resin was placed in a round-bottom flask that was fitted with a condenser and a nitrogen inlet. The flask was evacuated and filled with nitrogen. To this was added enough dry THF to just suspend the resin. Then 40 equivalents of 1 M BH_3/THF (based on resin loading) were added via syringe. The reaction mixture was heated to 65 °C with stirring and the suspension was maintained at reflux for 24 h. The suspension was cooled and poured into the appropriate PP vessel and drained. The resin was washed with 3 × THF and re-suspended in a small amount of THF. To this was added 2 ml/g resin DIPEA followed by 4 ml/g resin acetic acid and the suspension was

well mixed. This was followed by the addition of 20 equivalents of I_2 as a concentrated THF solution. The dark suspension was shaken vigorously on a shaker for 3.5-4 hours and then drained. The resin was washed with 3 × THF, 3 × Et_3N/DMF (1:3), 3 × MeOH, and finally 3 × CH_2Cl_2. The resulting resin was then dried *in vacuo* for > 12 h. The resin was suspended in THF and 105 equivalents of DIPEA were added followed by 100 equivalents of propionyl chloride added dropwise via syringe with good stirring. The resin was shaken for 3 days on a shaker at which point it was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2 and then dried *in vacuo* for > 12 h. Cleavage of a small sample of this resin with 5% TFA/CH_2Cl_2 afforded the triamide as its trifluoroacetate salt in a 74% yield.

^{1}H NMR (300 MHz, CD_3OD): δ: 7.45-7.10 (m, 5H), 4.2-2.8 (m, 13H), 2.47-2.20 (m, 4H), 2.20-1.80 (m, 3H), 1.48-0.60 (m, 17H)

ES-MS *m/z* $(M + H)^+$ = 461.3; LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50 % for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 10.426 min. % purity = >85%

4.3.5: Synthesis Of Tripeptide 90



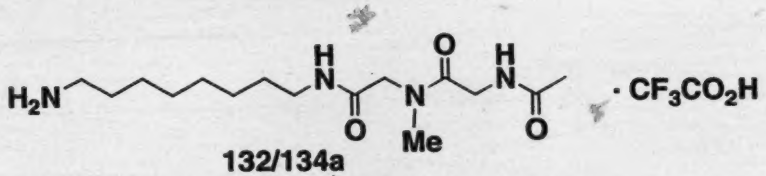
90

Tripeptide **90** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **90** as its trifluoroacetate salt in 90% yield.

^{1}H NMR (500 MHz, CD_3OD): δ (mixture of rotamers): 7.17-7.40 (m, 10H), 5.04-4.90 (dd, 1H, J_1 = 10.3 Hz, J_2 = 4.1 Hz), 4.70-4.54 (m, 2H), 4.46-4.36 (q, J = 7.2 Hz), 3.24-2.96 (m, 12H), 2.94 (s, 3H), 2.88 (s, 3H), 1.94 (s, 3H), 1.88 (s, 3H), 1.84-1.70 (m, 4H), 1.50-1.24 (m, 6H), 1.17 (d, 3 H, J = 7.1 Hz), 0.40 (d, 3H, J = 7.0 Hz)

ES-MS *m/z* $(M + H)^+ = 389.4$

4.3.6: Synthesis Of Tripeptide 132/134a



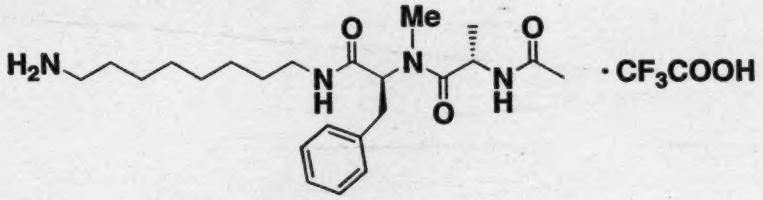
132/134a

Tripeptide **132** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **132** as its trifluoroacetate salt in 93% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 4.12-3.98 (m, 4H), 3.30-3.15 (m, 2H), 2.95-2.85 (m, 4H), 2.15 (s, 3H), 1.70-1.59 (m, 4H), 1.55-1.45 (m, 3H), 1.43-1.30 (m, 2H), 1.03-1.25 (m, 3H)

ES-MS *m/z* $(M + H)^+ = 315$

4.3.7: Synthesis Of Tripeptide 134b



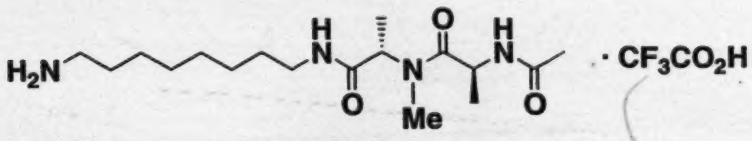
134b

Tripeptide **134b** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134b** as its trifluoroacetate salt in 76% yield.

^{1}H NMR (300 MHz, CD_3OD, mixture of rotamers): δ: 7.34-7.14 (m, 5H), 5.00 (dd, 1H, J_1= 4.1Hz, J_2= 11.2Hz), 4.88-4.80 (m, 1H), 4.69 –4.60 (q, 1H, J = 7.2Hz), 4.26 (q, 1H, J =7.3Hz), 3.28-3.22 (m, 2H), 3.20-3.16 (m, 2H), 3.14-3.09 (m, 2H), 3.08-3.00 (m, 2H), 2.98 (s, 3H), 2.94-2.84 (m, 12H), 1.90 (d, 3 H 1.70 –1.24 (m, 38)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 11.309 min.; *m/z* $(M + H)^+ = 419$; purity > 90%

4.3.8: Synthesis Of Tripeptide 134c



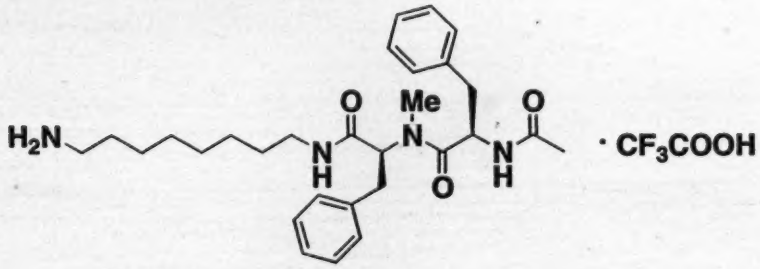
134c

Tripeptide **134c** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134c** as its trifluoroacetate salt in 75% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 4.91-4.85 (m, 1H), 4.75 (q, 1H, *J* = 7.1 Hz), 3.24-3.10 (m, 2H), 3.05 (s, 3H), 2.94-2.86 (m, 4H), 2.74 (s, 3H), 1.96-1.92 (m, 3H), 1.68-1.60 (m, 4H), 1.56-1.46 (m, 3H), 1.42-1.26 (m, 8H)

ES-MS *m/z* $(M + H)^+ = 343$

4.3.9: Synthesis Of Tripeptide 134d

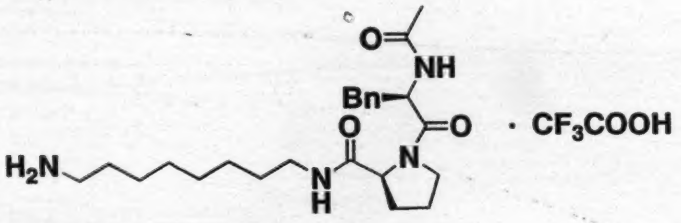


134d

Tripeptide **134d** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134d** as its trifluoroacetate salt in 94% yield.

^{1}H (500 MHz, CD_3OD): δ: 7.28-7.04 (m, 10H), 5.36 (dd, 1H, J_1 = 7.6, J_2 =11.4), 4.82 (m, 1H), 3.29-3.24 (m, 1H), 3.18-3.10 (m, 2H), 2.94- 2.86 (m, 5H), 2.78-2.72 (m, 1H), 2.59-2.44 (m, 2H), 1.88 (s, 3H), 1.68-1.59 (m, 3H), 1.48-1.42 (m, 2H), 1.40 (m, 10H).
LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 13.488 min. % purity > 95%. ES-MS *m/z* $(M + H)^+ = 495.3$

4.3.10: Synthesis Of Tripeptide 134e

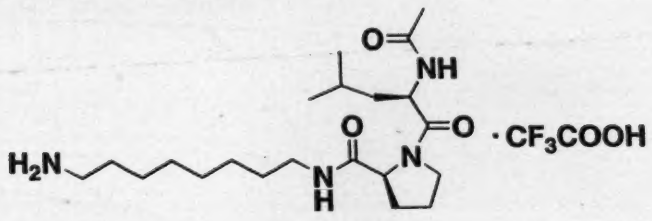


134e

Tripeptide **134e** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134e** as its trifluoroacetate salt in 96% yield.

^{1}H (500 MHz, CD_3OD, mixture of rotamers): δ: 7.32-7.16 (m, 10H), 4.58 (dd, 1H, J_1 = 7.0 Hz, J_2 = 9.3 Hz), 4.24 (dd, 1H, J_1 = 3.2 Hz, J_2 = 8.8 Hz), 3.64 (m, 1H), 3.54 (m, 1H), 3.60 (s, 3H), 3.22-3.14 (m, 2H), 3.12-3.04 (m, 4H), 3.02-2.96 (m, 4H), 2.94-2.86 (m, 4H), 2.70-2.60 (m, 1H), 2.20 (br s, 1H), 1.96 (s, 3H), 1.93-1.86 (m, 2H), 1.80-1.69 (m, 2H) 1.68-1.60 (m, 6H), 1.58-1.44 (m, 4H), 1.42-1.24 (m, 18H).
LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 11.351 min. ES-MS *m/z* $(M + H)^+ = 431$; % purity > 95%

4.3.11: Synthesis Of Tripeptide 134f



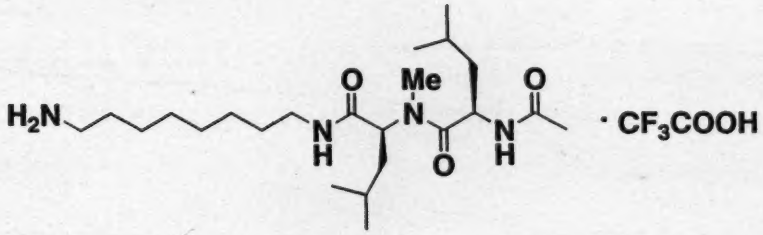
134f

Tripeptide **134f** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134f** as its trifluoroacetate salt in 84% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 5.00 (dd, 1H, J_1 = 5.5Hz, J_2 = 12.5 Hz), 4.38-4.30 (m, 1H), 3.98-3.90 (m, 1H), 3.64-3.44 (m, 2H), 3.13-3.04 (m, 2H), 2.92-2.85 (m, 4H), 2.04-1.96 (m, 3H), 1.94 (s, 3H), 1.70-1.56 (m, 7H), 1.40-1.24 (m, 16H)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 10.379, ES-MS *m/z* $(M + H)^+$ = 397.3; % purity> 82%

4.3.12: Synthesis Of Tripeptide 134g



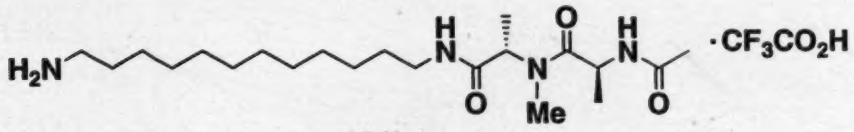
134g

Tripeptide **134g** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134g** as its trifluoroacetate salt in 90% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 5.12 (dd, 1H, J_1= 8.3 Hz, J_2 = 13.0 Hz), 4.71 (dd, 1H, J_1 = 6.4 Hz, J_2 = 12.0 Hz), 3.20-3.12 (m, 2H), 3.04 (s, 3H), 2.99-2.94 (m, 6H), 2.92-2.86 (m, 6H), 1.95 (s, 3H), 1.76-1.54 (m, 4H), 1.50-1.24 (m, 8H), 1.00-0.84 (m, 12H).

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 13.153, ES-MS *m/z* $(M + H)^+$ = 427.4; % purity > 76%

4.3.13: Synthesis Of Tripeptide 134h



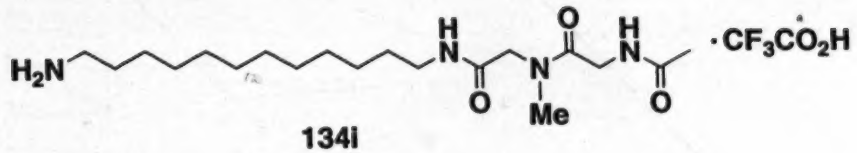
134h

Tripeptide **134h** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134h** as its trifluoroacetate salt in 97% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 4.94-4.85 (m, 1H), 4.80-4.70 (m, 1H), 3.20-3.10 (m, 2H), 3.05 (s, 3H), 2.90 (t, 2H, J = 7.5 Hz), 1.95 (s, 3H), 1.70-1.56 (m, 3H), 1.54-1.44 (m, 2H), 1.42-1.24 (m, 23 H)

LC-MS: Zorbax Rx-C8 4.6 × 50 mm, 3.5 μm; 0–50% MeCN (0.1% TFA), H_2O (0.1% TFA) for 8 minutes maintained at 50% for 12 minutes; flow: 0.7 ml/min., DAD detector. Rt = 15.723 min. ES-MS *m/z* $(M + H)^+$ = 398.3

4.3.14: Synthesis Of Tripeptide 134 i



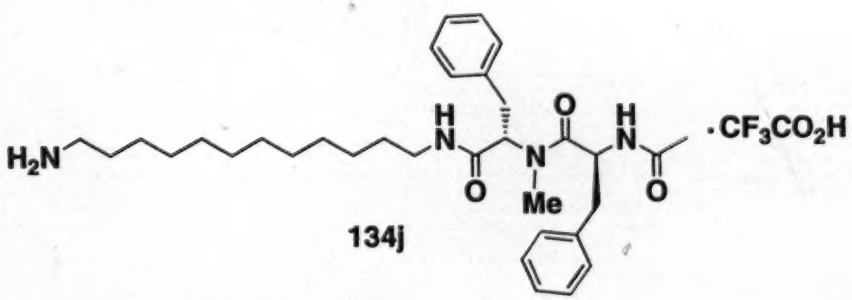
134i

Tripeptide **134i** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134i** as its trifluoroacetate salt in 84% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 4.10 (s, 3H), 4.04 (s, 2H), 3.25-3.16 (m, 2H), 3.06 (s, 3H), 2.94-2.88 (s, 3H), 2.02 (s, 3H), 1.68-1.60 (s, 3H), 1.54-1.46 (m, 2H), 1.42-1.28 (m, 16H)

ES-MS *m/z* $(M + H)^+ = 371.3$

4.3.15: Synthesis Of Tripeptide 134j



134j

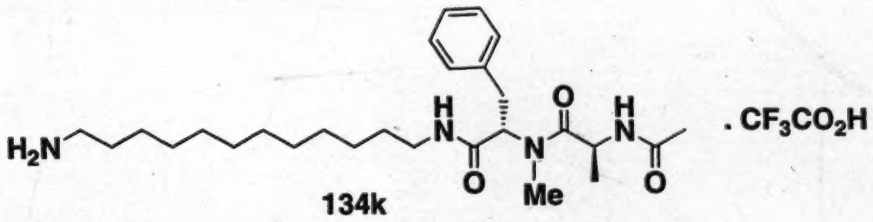
Tripeptide **134j** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134j** as its trifluoroacetate salt in 94% yield.

^{1}H NMR (500 MHz, CD_3OD): δ (mixture of rotamers ~ 1:1 ratio): 7.25-7.00 (m, 20H), 5.10 (dd, 1H, $J_1 = 5.4$ Hz, $J_2 = 6.1$ Hz), 5.02 (dd, 1H, $J_1 = 4.3$ Hz, $J_2 = 6.7$ Hz), 4.96 (dd, 1H, $J_1 = J_2 = 5.5$ Hz), 4.78 (dd, 1H, $J_1 = 4.3$ Hz, $J_2 = 7.3$ Hz), 3.26-3.18 (m, 2H), 3.18-

3.04 (m, 4H), 2.98-2.82 (m, 14 H), 2.60-2.52 (m, 2H), 1.84 (s, 3H), 1.82 (s, 3H), 1.68-1.60 (m, 6H), 1.48-1.18 (m, 40H)

ES-MS *m/z* $(M + H)^+$ = 551.3; LC-MS: Zorbax Rx-C8 4.6 × 50 mm, 3.5 μm; 0–50% MeCN (0.1% TFA), H_2O (0.1% TFA) for 8 minutes maintained at 50% for 12 minutes; flow: 0.7 ml/min., DAD detector. Rt = 15.862 min.; % purity > 95%

4.3.16: Synthesis Of Tripeptide 134k



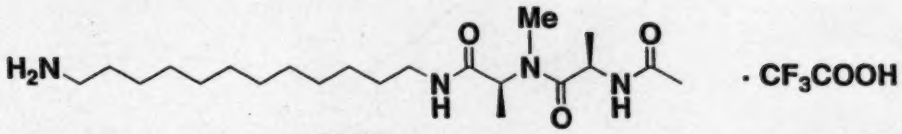
134k

Tripeptide **134k** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134k** as its trifluoroacetate salt in 95% yield.

^1H NMR (500 MHz, CD_3OD): δ (mixture of rotamers): 7.40-7.15 (m, 10H), 5.00 (dd, 1H, J_1 = 3.4 Hz, J_2 = 11.4 Hz), 4.88 (dd, 1H, $J_1 = J_2$ = 8.0 Hz), 4.66 (dd, 1H, J_1 = 6.8 Hz, J_2, 13.6 Hz), 4.36 (dd, 1H, J_1 = 6.8 Hz, J_2 = 14.8 Hz), 3.21-3.00 (m, 10H), 2.94-2.84 (m, 10H), 1.92 (s, 3H), 1.88 (s, 3H), 1.68-1.58 (m, 6H), 1.56-1.46 (m, 2H), 1.44-1.22 (m, 40H)

ES-MS *m/z* $(M + H)^+$ = 475.2; LC-MS: Zorbax Rx-C8 4.6 × 50 mm, 3.5 μm; 0–50% MeCN (0.1% TFA), H_2O (0.1% TFA) for 12 minutes maintained at 50% for 8 minutes; flow: 0.7 ml/min., DAD detector. Rt = 15.975 min. % purity > 90%

4.3.17: Synthesis Of Tripeptide 134l



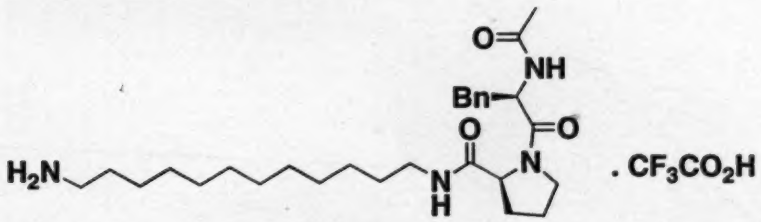
134l

Tripeptide **134l** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134l** as its trifluoroacetate salt in 85% yield.

^1H (500 MHz, CD_3OD): δ: 5.7 (q, 1H, *J1* = 6.4 Hz), 4.69 (q, 1H, J_1 = 6 Hz), 3.17 (t, 2H, *J* = 8.8 Hz), 3.04 (s, 3H), 2.9 (m, 4H), 1.88 (s, 3H), 1.68-1.60 (m, 5H), 1.54 – 1.44 (m, 4H), 1.42-1.24 (m, 23H)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 11.90 min, ES-MS *m/z* $(M + H)^+$ = 399; % purity > 90 %

4.3.18: Synthesis Of Tripeptide 134m



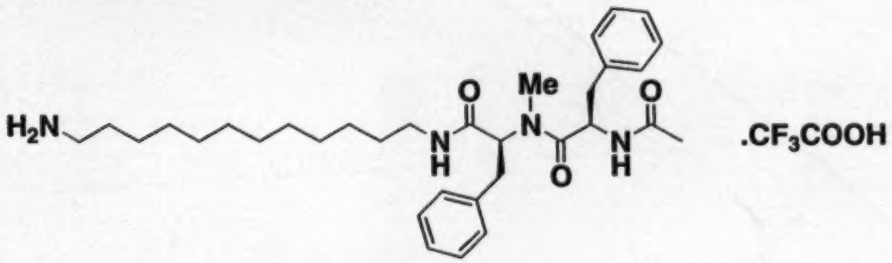
134m

Tripeptide **134m** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134m** as its trifluoroacetate salt in 97% yield.

^1H NMR (500 MHz, CD_3OD): δ: 7.32-7.14 (m, 5H), 4.58 (dd, 1H, J_1 = 6.3 Hz, J_2 = 9.4 Hz), 4.24 (dd, 1H, J_1 = 3.1 Hz, J_2 = 7.8 Hz), 3.18-3.06 (m, 2H), 3.20-2.96 (m, 2H), 2.92-2.86 (m, 3H), 1.94 (s, 3H), 1.80-1.68 (m, 2H), 1.68-1.58 (m, 2H), 1.56-1.42 (m, 3H), 1.42-1.22 (m, 20H)

ES-MS *m/z* $(M + H)^+$ = 487.3; LC-MS: Zorbax Rx-C8 4.6 × 50 mm, 3.5 µm; 0–50% MeCN (0.1% TFA), H_2O (0.1% TFA) for 12 minutes maintained at 50% for 8 minutes; flow: 0.7 ml/min., DAD detector. Rt = 13.09 min.; % purity > 95 %

4.3.19: Synthesis Of Tripeptide 134n



134n

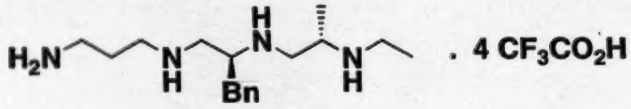
Tripeptide **134n** was prepared according to general procedure 4.1.2. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **134n** as its trifluoroacetate salt in 86% yield.

^{1}H NMR (500 MHz, CD_3OD):δ: 7.35-7.40 (m, 10H), 5.24 (dd, 1H, J_1 = 6.4 Hz, J_2 = 9.6 Hz), 3.29-3.24 (m, 1H), 3.18-3.09 (m, 2H), 2.92-2.86 (m, 6H), 2.79-2.74 (m, 1H), 2.59-2.46 (m, 2H), 2.14 (s, 3H), 1.88 (s, 3H), 1.68-1.60 (m, 4H), 1.48-1.30 (m, 17H)

ES-MS *m/z* $(M + H)^+$ = 551.4; LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector; Rt = 15.65; % purity > 95 %

4.4: Synthesis Of Oligoamines

4.4.1: Synthesis Of Tetramine 110



110

Oligoamine **110** was prepared according to general procedure 4.1.3. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **110** as its *tetrakis*(trifluoroacetate) salt in 95% yield.

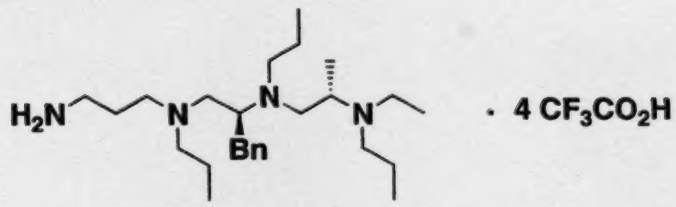
IR (methanol cast) 3001 (N-H stretches), 1675, 1202, 1131, 799, 721 cm^{-1}; $[\alpha]_D$ = (+) 1.46° (c = 76.8 mg/mL in MeOH);

^1H NMR (300 MHz, CD_3OD): δ ppm: 7.38 - 7.18 (m, 5H), 3.24 - 2.84 (m, 12H), 2.79 (dd, J_1 = 4.2, J_2 = 13.5 Hz, 1H), 2.63 (dd, J_1 = 7.8, J_2 =13.5 Hz, 1H), 2.20 - 2.00 (m, 2H), 1.31 (t, J = 7.3 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H).

^{13}C NMR (APT, 75.5 MHz, CD_3OD): δ ppm: 138.5 (C), 130.3 (CH), 129.9 (CH), 127.9 (CH), 58.2 (CH), 54.9 (CH), 52.2 (CH_2), 49.2 (CH_2), 45.9 (CH_2), 41.3 (CH_2), 39.5 (CH_2), 37.8 (CH_2), 25.2 (CH_2), 14.8 (CH_3), 11.5 (CH_3).

LC-MS: Zorbax XDB-C8 (4.6 × 50 mm, 3.5 μm); eluent: 10 % acetonitrile (0.1 % TFA) and 90% water (0.1% TFA) to 20% acetonitrile over 15 minutes at 0.700 mL/min; column temperature: 20 °C; detection: UV diode array at 250 nm. Rt = 8.109 min. % purity = 82%; ES-MS *m/z* $(M + H)^+$ = 293.5; HRMS for $C_{17}H_{33}N_4$ (MH^+) calcd. 293.2705, found 293.2715

4.4.2: Synthesis Of Tetramine 116



116

The tripeptide containing resin was placed in a round-bottom flask that was fitted with a condenser and a nitrogen inlet. The flask was evacuated and filled with nitrogen. To this was added enough dry THF to just suspend the resin. Then 40 equivalents of 1 M BH_3/THF (based on resin loading) were added via syringe. The reaction mixture was heated to 65 °C with stirring and the suspension was maintained at reflux for 24 h. The suspension was cooled and poured into the appropriate PP vessel and drained. The resin was washed with 3 × THF, and then 3 × DMF and was suspended in DMF. To this suspension was added 50 equivalents of isobutyraldehyde as a DMF solution. This was immediately followed by the addition of 55 equivalents of sodium triacetoxyborohydride as a DMF solution. The resulting suspension was left on the shaker for 48 h at which point the resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. The resin was then dried *in vacuo* for > 12 h. Cleavage of a small sample of the resin with 5% TFA/CH_2Cl_2 afforded the oligo-*tert*-amine as its *tetrakis*(trifluoracetate) salt in 83% yield.

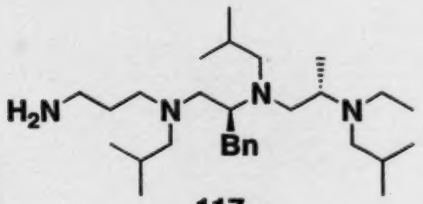
IR (MeOH cast) in cm^{-1}: 3300-2600 (N-H stretch), 1674.36 (C=O, TFA salt), 1202.64 (C-N stretch), 1133.99 (C-N stretch)

^{1}H NMR (300 MHz, CD_3OD): δ: 7.45-7.20 (m, 5H), 3.6-2.52 (m, 17H), 2.18-1.86 (m, 3H), 1.82-1.42 (m, 4H), 1.44-1.16 (m, 11H), 1.10-0.90 (m, 9H)

^{13}C NMR (APT, 75.5 MHz, CD_3OD): δ: 139.6 (C), 130.5 (CH), 129.9 (CH), 128.0 (CH), 62.2 (CH), 58.4 (CH), 55.0 (CH_2), 52.0 (CH_2), 49.9 (CH_2), 46.1 (CH_2), 39.6 (CH_2), 37.77 (CH_2), 35.7 (CH_2), 27.6 (CH_2), 26.0 (CH_2), 25.2 (CH_2), 23.1 (CH_2), 19.7 (CH_2), 19.2 (CH_2), 12.1 (CH_3), 12.0 (CH_3), 11.2 (CH_3), 11.0 (CH_3), 10.6 (CH_3).

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 4.581 min.; % purity = 71%; ES-MS *m/z* $(M + H)^+$ = 419.5; HRMS (ES) for $C_{26}H_{51}N_4$ (MH^+) calcd 419.4114, found 419.4107

4.4.3: Synthesis Of Tetramine 117



· 4 CF_3CO_2H

117

The synthesis of tetramine **117** was exactly as described above. Cleavage of a small sample of this resin with 5% TFA/CH_2Cl_2 afforded the oligo-*tert*-amine as its *tetrakis*(trifluoroacetate) salt in 96 % yield.

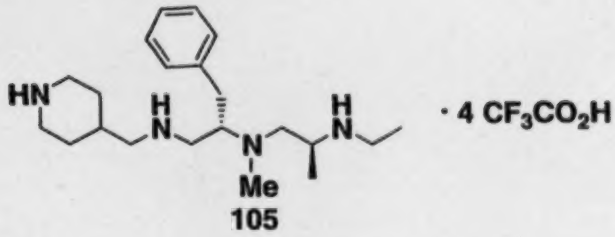
IR (MeOH cast) cm^{-1} 3300-2600 (N-H stretch), 1674.38 (C=O, TFA salt), 1202.66 (C-N stretch), 1134.52 (C-N stretch)

^1H NMR (CD_3OD, 300 MHz) δ: 7.40-7.18 (m, 5H), 3.6-2.70 (m, 13H), 2.55-2.45 (m, 1H), 2.40-2.25 (m, 1H), 2.20-1.85 (m, 4H), 1.8-1.6 (m, 1H), 1.5-0.78 (m, 29H).

^{13}C NMR (APT, CD_3OD, 75.5 MHz) δ: 139.7 (C), 130.4 (2 × CH), 129.9 (2 × CH), 127.9 (CH), 63.1 (CH), 61.2 (CH), 60.5 (CH), 56.8 (CH_2), 53.3 (CH_2), 52.0 (CH_2), 46.4(CH_2), 39.8 (CH_2), 37.9 (CH_2), 37.3 (CH_2), 28.0 (CH_3), 26.2 (CH_3), 25.8 (CH_3), 25.6 (CH_3), 25.2 (CH_2), 22.9 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 20.6 (CH_3), 11.7 (CH_3), 10.3 (CH_3).

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 6.258 min.; % purity = 70%; ES-MS *m/z* $(M + H)^+$ = 461.5; HRMS for $C_{29}H_{57}N_4$ (MH^+) calcd 461.4582, found 461.4577.

4.4.4: Synthesis Of Tetramine 105



105

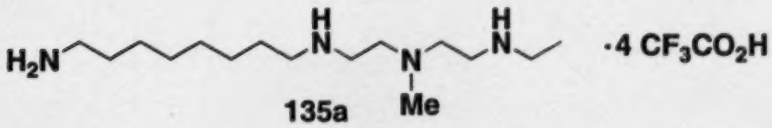
Oligoamine **105** was prepared according to general procedure 4.1.3. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **105** as its *tetrakis*(trifluoroacetate) salt in 85% crude yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 7.42-7.20 (m, 5H), 3.70-2.50 (m, 12H), 2.40 (s, 3H), 2.20-1.93 (m, 3H), 1.25-1.40 (m, 12H)

^{13}C NMR (125 MHz, CD_3OD): δ: 139.4 (C), 130.2 (CH), 129.9 (CH), 127.8 (CH), 64.5 (CH_2), 53.5 (CH_2), 52.9 (CH), 48.9 (CH_2), 45.2 (CH_2), 45.3 (CH_2), 45.4 (CH_2), 44.8 (CH_2), 44.7 (CH_2), 41.5 (CH_2), 33.0 (CH_2), 32.5 (CH_3), 27.5 (CH_2), 14.5 (CH_3), 11.5 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 7 min. maintained at 50 for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 10.945 min.; % purity = >90%; ES-MS *m/z* $(M + H)^+ = 347.3$

4.4.5: Synthesis Of Tetramine 135a

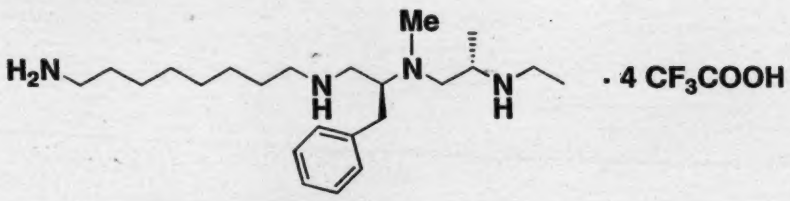


135a

Oligoamine **135a** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135a** as part of a complex mixture of products.

ES-MS *m/z* $(M + H)^+ = 273$

4.4.6: Synthesis Of Tetramine 135b



135b

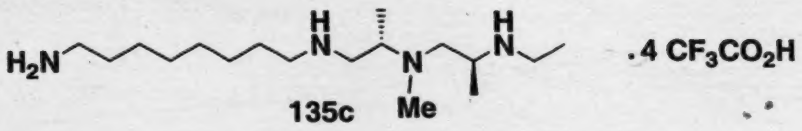
Oligoamine **135b** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135b** as its *tetrakis*(trifluoroacetate) salt in 74% yield.

^{1}H NMR (400 MHz, CD_3OD): δ: 7.32-7.18 (m, 5H), 3.44-3.34 (m, 1H), 3.13- 3.12 (m, 2H), 3.22-3.10 (m, 3H), 2.95-2.84 (m, 3H), 2.82-2.66 (m, 3H), 2.58-2.50 (m, 1H), 2.34 (s, 3H), 1.68-1.56 (m, 4H), 1.38-1.22 (m, 14H)

^{13}C NMR (100 MHz, CD_3OD, APT): δ: 139.5 (C), 130.3 (CH), 130.0 (CH), 127.9 (CH), 73.5 (CH_2), 64.6 (CH), 62.2 (CH_2), 58.4 (CH_2), 58.4 (CH_2), 53.0 (CH_2), 41.1 (CH_2), 40.7 (CH_2), 37.0 (CH_3), 33.0 (CH_2), 29.9 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 14.5 (CH_3), 11.5 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 9.892 min.; % purity > 99%; ES-MS *m/z* $(M + H)^+ = 377.2$; HRMS: for $C_{23}H_{45}N_4$ (MH^+) 377.3639 found 377.3639

4.4.7: Synthesis Of Tetramine 135c



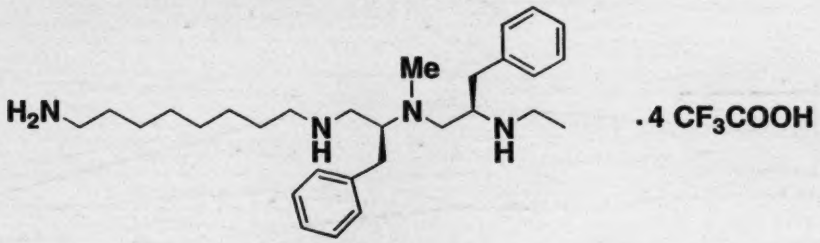
135c

Oligoamine **135c** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135c** as its *tetrakis*(trifluoroacetate) salt in 74% crude yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 3.22-3.12 (m, 2H), 2.98-2.80 (m, 2H), 2.80-2.60 (m, 3H), 2.40-2.20 (m, 3H), 1.92 (s, 3H), 1.68-1.46 (m, 4H), 1.42-1.26 (m, 11H), 1.26-1.13 (m, 4H), 1.13-1.06 (m, 2H), 0.98-0.86 (m, 2H)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 6.767 min; % purity = 65%; ES-MS *m/z* $(M + H)^+ = 301$

4.4.8: Synthesis Of Tetramine 135d



135d

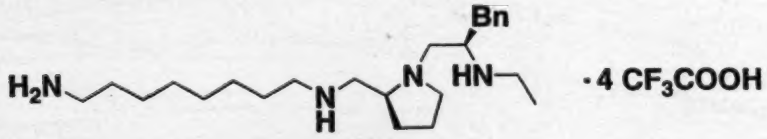
Oligoamine **135d** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135d** as its *tetrakis*(trifluoroacetate) salt in 91% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 7.35-7.12 (m, 10H), 3.25-3.06 (m, 4H), 3.04-2.78 (m, 8H), 2.71-2.62 (m, 2H), 2.58-2.44 (m, 2H), 2.10 (s, 3H), 1.70-1.56 (m, 6H), 1.44-1.22 (m, 14H)

^{13}C (APT, 75 MHz, CD_3OD) δ: 139.4 (C), 137.0 (C), 130.2 (CH), 130.1 (CH), 129.9 (CH), 128.3 (CH), 127.9 (CH), 65.6 (CH), 59.6 (CH_2), 56.8 (CH), 40.7 (CH_2), 40.6 (CH_2), 35.8(CH_2), 33.3 (CH_2), 32.6 (CH_3), 29.8 (3 x CH_2), 28.5 (CH_2), 27.3 (2 × CH_2), 27.2 (CH_2), 26.9 (CH_2) 11.7 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt= 17.64 min; % purity = 91.96%; ES-MS *m/z* $(M + H)^+$ = 435.4; HRMS: cald'd for $C_{29}H_{49}N_4$ (MH^+) = 435.3957, found 453.3954

4.4.9: Synthesis Of Tetramine 135e



135e

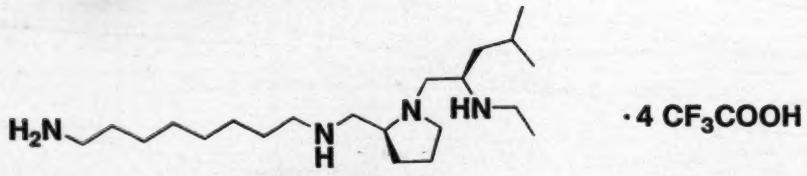
Oligoamine **135e** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135e** as its *tetrakis*(trifluoroacetate) salt in 73% yield.

^1H NMR (500 MHz, CD_3OD): δ: 7.37-7.25 (m, 5H), 3.64-3.56 (m, 1H), 3.29-3.24 (m, 2H), 3.22-3.08 (m, 3H), 3.60-3.00 (m, 4H), 2.99-2.94 (m, 1H), 2.90 (t, 2H, *J*= 7.5 Hz), 2.76 (dd, 1H, J_1 = 8.7 Hz, J_2 = 12.5 Hz), 2.55 (dd, 1H, J_1 = 5.1 Hz, J_2 = 12.5 Hz), 2.18-2.10 (m, 1H), 2.05-1.98 (m, 1H), 1.8-1.6 (m, 8H), 1.44-1.30 (m, 12H)

^{13}C (BB, 75 MHz, CD_3OD): δ: 137.06 (C), 130.2 (CH), 130.1 (CH), 128.5 (CH), 63.0 (CH), 58.0 (CH_2), 57.1 (CH), 53.8 (CH_2), 51.4 (CH_2), 41.6 (CH_2), 41.3 (CH_2), 36.1 (CH_2), 30.0 (2 × CH_2), 29.4 (CH_2), 28.9 (CH_2), 28.5 (CH), 27.5 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 23.9 (CH_2), 11.5 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 10.334; purity > 86%; ES-MS *m/z* $(M + H)^+$ = 389.4; HRMS calcd for $C_{24}H_{45}N_4$ (MH^+) 389.3639 found 389.3645

4.4.10: Synthesis Of Tetramine 135f



135f

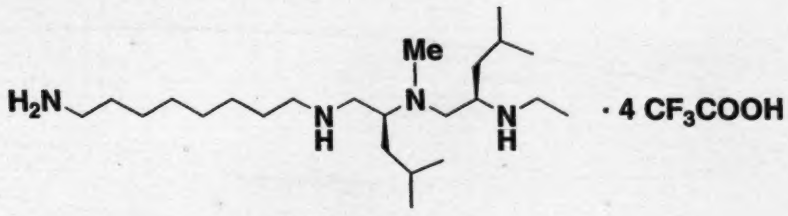
Oligoamine **135f** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135f** as its *tetrakis*(trifluoroacetate) salt in 80% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 3.36-3.26 (m,1H), 3.26-3.14 (m, 3H), 3.14-3.06 (m, 3H), 3.06-3.00 (m, 2H), 2.90-2.79 (m, 5H), 2.54-2.46 (m, 1H), 2.20-2.08 (m, 1H), 2.00-1.82 (m, 2H), 1.80-1.58 (m,6H), 1.50-1.24 (m, 16H), 1.00-1.92 (m, 6H)

^{13}C NMR (100 MHz, CD_3OD): δ: 63.3 (CH), 57.5 (CH_2), 55.4 (CH), 54.0 (CH_2), 51.1 (CH_2), 49.9 (CH_2), 44.2 (CH_2), 40.7 (2 × CH_2), 38.7 (CH_2), 29.8 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 26.1 (CH), 23.9 (CH_2), 23.7 (CH_3), 21.7 (CH_3), 11.5 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 13.493 min. % purity > 63%; ES-MS *m/z* $(M + H)^+$ = 355.6; HRMS for $C_{21}H_{47}N_4$ (MH^+) calcd 355.3795 found 355.3796

4.4.11: Synthesis Of Tetramine 135g



135g

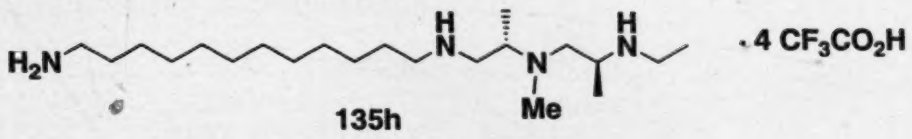
Oligoamine **135g** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135g** as its *tetrakis*(trifluoroacetate) salt in 77 % yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 3.38-3.28 (m, 2H), 3.24-3.16 (m, 1H), 3.12 (2.94 (m, 4H), 2.92-2.78 (m, 5H), 2.64-2.50 (m, 1H), 2.10 (s, 3H), 1.80-1.48 (m, 8H), 1.44-1.18 (m, 16H), 1.0-0.86 (m, 8H)

^{13}C NMR (100 MHz, CD_3OD): δ: 61.5 (CH), 59.7 (CH_2), 54.1 (CH), 50.4 (CH_2), 44.0 (CH_2), 40.1 (CH_2), 38.4 (CH_2), 35.2 (CH_2), 32.5 (CH/CH_3), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 27.3 (CH_2), 27.0 (CH_2), 26.3 (CH/CH_3), 26.2 (CH/CH_3), 24.0 (CH/CH_3), 23.7 (CH/CH_3), 22.0 (CH/CH_3), 21.7 (CH/CH_3), 11.6 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt= 12.392 min. % purity > 85%; ES-MS *m/z* $(M + H)^+$ = 385.4; HRMS for $C_{23}H_{53}N_4$ (MH^+) calcd 385.4265 found 385.4266

4.4.12: Synthesis Of Tetramine 135h



135h

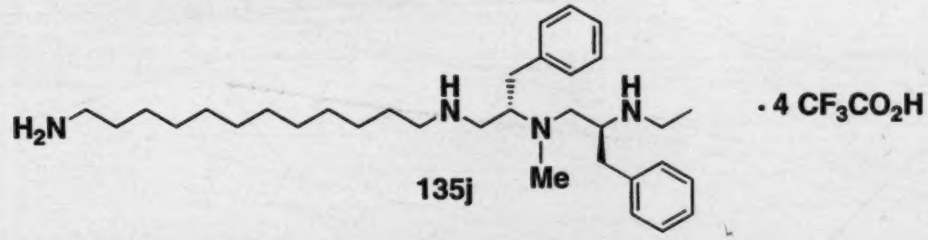
Oligoamine **135h** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135h** as its *tetrakis*(trifluoroacetate) salt in 76% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 3.64-.356 (m, 1H), 3.26-3.16 (m, 2H), 3.16-2.96 (m, 4H), 2.96-2.86 (m, 4H), 2.78-2.86 (m, 4H), 2.78-2.58 (m, 1H), 2.23 (s, 3H), 1.78-1.68 (m, 2H), 1.68-1.58 (m, 4H), 1.52-1.24 (m, 20H), 1.08-1.03 (m, 2H)

^{13}C NMR (125 MHz, CD_3OD): δ: 57.8 (CH_2), 57.3 (CH), 53.0 (CH), 41.1 (CH), 40.8 (CH_2), 36.8 (CH_3), 30.6 (CH_2), 30.5 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 30.4 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 20.6 (CH_2), 27.6 (CH_2), 27.4 (CH_2), 26.9 (CH_2), 14.5 (CH_3), 11.5 (CH_3), 10.0 (CH_3)

LC-MS: Zorbax Rx-C8 4.6 × 50 mm, 3.5 μm; 0 –50% MeCN (0.1% TFA), H_2O (0.1% TFA) for 8 minutes maintained at 50% for 7 minutes; flow rate: 0.7 ml/min., DAD detector; Rt = 8.22 min., purity = 68.9%; ES-MS *m/z* $(M + H)^+$ = 357.4; HRMS for $C_{21}H_{49}N_4$ (MH^+) calcd 357.3957 found 357.3947

4.4.13: Synthesis Of Tetramine 135j



135j

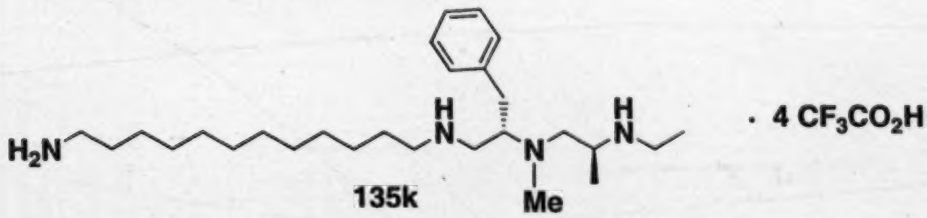
Oligoamine **135i** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135i** as its *tetrakis*(trifluoroacetate) salt in 88% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 7.42-6.72 (m, 10 H), 3.58-3.48 (m, 1H), 3.21-3.09 (m, 2H), 3.04-2.96 (m, 1H), 2.92-2.80 (m, 5H), 2.79-2.36 (m, 4H), 2.36 (dd, 1H, J_1 = 10.1 Hz, J_2 = 15.0 Hz), 2.27 (s, 3H), 1.70-1.52 (m, 4H), 1.40-1.20 (m, 20 H)

^{13}C NMR (APT, 125 MHz, CD_3OD): δ: 139.2 (C), 137.3 (C), 130.5 (CH), 130.3 (CH), 130.0 (CH), 129.9 (CH), 128.5 (CH), 127.7 (CH), 62.8 (CH), 58.9 (CH), 55.7 (CH_2), 48.0 (CH_2), 41.5 (CH_2), 40.8 (CH_2), 36.5 (CH_2), 35.4 (CH_2), 32.6 (CH_2), 30.6 (CH_2), 30.5 (2 × CH_2), 30.4 (CH_2), 30.4 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 28.6 (CH_2), 27.5 (CH_2), 27.4 (CH_2), 26.9 (CH_2), 11.7 (CH_3)

LC-MS: Zorbax Rx-C8 4.6 × 50 mm, 3.5 μm; 0 –50% MeCN (0.1% TFA), H_2O (0.1% TFA) for 12 minutes maintained at 50% for 8 minutes; flow rate: 0.7 ml/min., DAD detector. Rt = 13.996 min.% purity > 95%; ES-MS *m/z* $(M + H)^+$ = 509.5; HRMS for $C_{33}H_{57}N_4$ (MH^+) calcd 509.4583 found 509.4587

4.4.14: Synthesis Of Tetramine 135k



135k

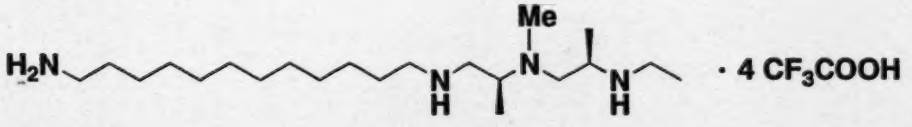
Oligoamine **135k** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135k** as its *tetrakis*(trifluoroacetate) salt in 98% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 7.38-7.18 (m, 5H), 3.18-3.06 (m, 2H), 3.05-2.84 (m, 6H), 2.82-2.40 (m, 7H), 1.68-1.50 (m, 4H), 1.42-1.20 (m, 24H)

^{13}C NMR (125 MHz, CD_3OD): δ: 139.5 (C), 130.2 (CH), 129.9 (CH), 127.8 (CH), 64.6 (CH), 64.6 (CH_3), 58.3 (CH_2), 53.0 (CH), 41.3 (CH_2), 40.9 (CH_2), 33.1 (CH_2), 30.7 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 27.6 (CH_2), 27.5 (CH_2), 14.6 (CH_3), 11.6 (CH_3)

LC-MS: Zorbax Rx-C8 4.6 × 50 mm, 3.5 µm; 0–50% MeCN (0.1% TFA), H_2O (0.1% TFA) for 7 minutes maintained at 50% for 8 minutes; flow rate: 0.7 ml/min., DAD detector. Rt = 9.94 min.; % purity = 69.84 %; ES-MS *m/z* $(M + H)^+$ = 475.2; HRMS for $C_{27}H_{53}N_4$ (MH^+) calcd 433.4270, found 433.4262

4.4.15: Synthesis Of Tetramine 135l



135l

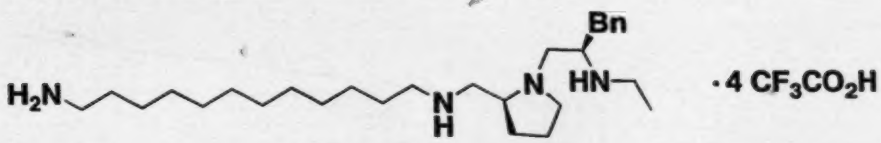
Oligoamine **135 l** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135l** as its *tetrakis*(trifluoroacetate) salt in 84% yield.

^1H NMR (500 MHz, CD_3OD):δ: 3.52-3.44 (m, 1H), 3.24-3.12 (m, 4H), 3.10-3.00 (m, 4H), 2.96-2.86 (m, 4H), 2.74 (dd, 1H, J_1 = 4.5 Hz, J_2 = 13.6 Hz), 2.67-2.59 (m, 1H), 2.12 (s, 3H), 1.78-1.68 (m, 2H), 1.68-1.16 (m, 3H), 1.42-1.26 (m, 25 H)

^{13}C NMR (75 MHz, CD_3OD): δ: 61.1 (CH), 58.4 (CH), 52.3 (CH_2), 51.9 (CH_2), 40.8 (CH_2), 40.3 (CH_2), 32.4 (CH_3), 30.6 (CH_2), 30.5 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 30.4 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 28.6 (CH_2), 27.6(CH_2), 27.4 (CH_2), 27.0 (CH_2), 14.2 (CH_3), 11.5 (CH_3), 9.8 (CH_3).

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 10.408; % purity> 92 %; ES-MS *m/z* $(M + H)^+$ = 357.4; HRMS: for $C_{21}H_{49}N_4$ (MH^+) calcd 357.3952 found 357.3954

4.4.16: Synthesis Of Tetramine 135m



135m

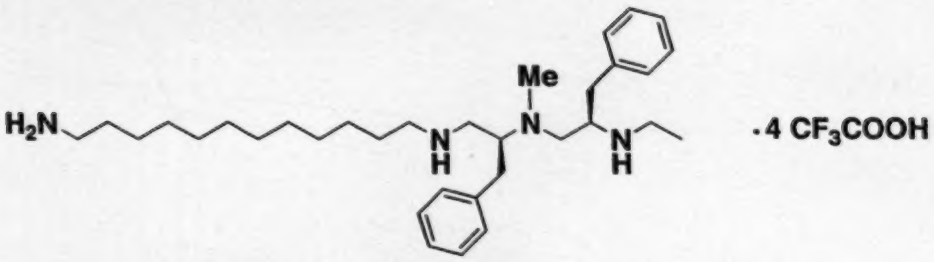
Oligoamine **135m** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135m** as its *tetrakis*(trifluoroacetate) salt in 82% yield.

^{1}H NMR (500 MHz, CD_3OD): δ: 7.42-7.24 (m, 5H), 3.28-3.10 (m, 4H), 3.10-2.94 (m, 4H), 2.94-2.86 (m, 3H), 2.70 (dd, 1H, J_1 = 4.8 Hz, J_2 = 7.1 Hz), 2.57 (dd, 1H, J_1 = 2.4 Hz, J_2 = 7.1 Hz), 2.18-1.98 (m, 2H), 1.80-1.60 (m, 8Hz), 1.42-1.22 (m, 20H)

^{13}C NMR (125 MHz, CD_3OD): δ: 139.9 (C), 130.20 (CH), 130.1 (CH), 128.5 (CH), 63.3 (CH), 58.1 (CH), 57.0 (CH_2), 53.9 (CH_2), 51.2 (CH_2), 50.0 (CH_2), 41.5 (CH_2), 40.9 (CH_2), 36.2 (CH_2), 30.7 (CH_2), 30.7 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 27.0 (CH_2), 23.9 (CH_2), 11.7 (CH_3)

LC-MS: Zorbax Rx-C8 4.6 × 50 mm, 3.5 μm; 0 –50% MeCN (0.1% TFA), H_2O (0.1% TFA) for 12 minutes maintained at 8 minutes; flow: 0.7 ml/min., DAD detector. Rt = 12.32 min.; % purity > 90%; ES-MS *m/z* $(M + H)^+$ = 445.4; HRMS for $C_{28}H_{53}N_4$ (MH^+) calcd 445.4265 found 445.4267

4.4.17: Synthesis Of Tetramine 135n



135n

Oligoamine **135n** was prepared according to general procedure 4.1.4. Cleavage of a small portion of the resin with 5% TFA/CH_2Cl_2 afforded **135n** as its *tetrakis*(trifluoroacetate) salt in 78% yield.

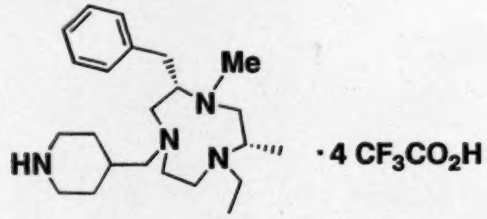
^{1}H NMR (500 MHz, CD_3OD): δ: 7.34-7.14 (m, 10), 3.60-3.54 (m, 1H), 3.36-3.08 (m, 3H), 3.04-2.78 (m, 8H), 2.70-2.62 (m, 2H), 2.56-2.48 (m, 2H), 2.12 (s, 3H), 1.70-1.58 (m, 6H), 1.42-1.24 (m, 17H)

^{13}C NMR (75 MHz, CD_3OD): δ: 139.4 (C), 137.0 (C), 130.4 (CH), 130.2 (CH), 130.1 (CH), 129.9 (CH), 128.3 (CH), 127.9 (CH), 65.5 (CH), 59.6 (CH), 56.8 (CH), 40.8 (CH_2), 40.8 (CH_2), 40.6 (CH_2), 35.8 (CH_2), 33.3 (CH_2), 32.6 (CH_3), 30.6 (CH_2), 30.5 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 30.22 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 28.6 (CH_2), 27.5 (CH_2), 27.4 (CH_2), 27.0 (CH_2) 11.7 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes; flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 14.402; % purity> 88 %; ES-MS *m/z* $(M + H)^+$ = 509.5; HRMS: for $C_{33}H_{57}N_4$ (MH^+) calcd 509.4578, found 509.4571

4.5: Synthesis Of Azacycloalkanes

4.5.1: Synthesis Of Triazacyclononane 150



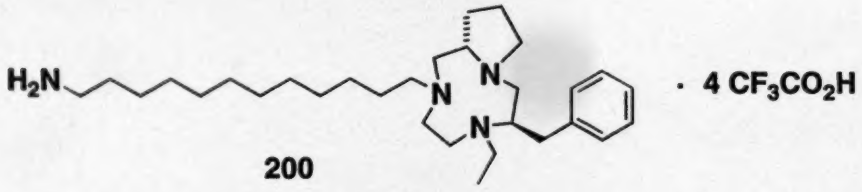
150

Compound **150** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded crude **150** as its *tetrakis*(trifluoroacetate) salt in 77% crude yield.

^{1}H NMR (300 MHz, CD_3OD): δ: 7.50-7.20 (m, 5H), 4.60-3.65 (m, 4H), 3.65-3.40 (m, 4H), 3.30-2.80 (m, 8H), 2.80-2.60 (m, 2H), 2.50-2.20 (m, 2H), 2.20-1.70 (m, 3H), 1.70-1.60 (m, 1H), 1.65-1.02 (m, 10H)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes; flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 11.297 min.; % purity (crude) = 35%; ES-MS *m/z* $(M + H)^+$ = 373.3

4.5.2: Synthesis Of Triazacyclononane 200



200

Compound **200** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded **200** as its *tetrakis*(trifluoroacetate) salt, in a 3:1 mixture with its quaternary piperazinium analogue (LC-MS) as the minor component,

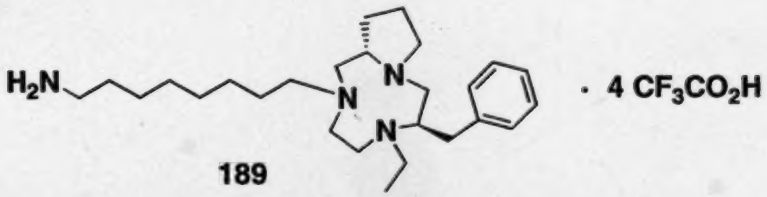
which was purified by semi-preparative HPLC and isolated as its *tetrakis*(trifluoroacetate) salt in 17% overall yield from its corresponding peptide.

^{1}H NMR (500 MHz, CD_3OD): δ: 7.46-7.24 (m, 5H), 4.18-4.06 (m, 2H), 3.90-3.74 (m, 2H), 3.74-3.56 (m, 3H), 3.56-3.36 (m, 3H), 3.30-3.14 (m, 2H), 3.06-2.94 (m, 3H), 2.70 (t, 2H, J = 6.8Hz), 2.83-2.76 (m, 1H), 2.68-2.53 (m, 2H), 2.27-2.14 (m, 2H), 2.12-2.01 (m, 1H), 1.77-1.68 (m, 1H), 1.68-1.57 (m, 3H), 1.56- 1.47 (m, 2H), 1.44-1.24 (m, 20H)

^{13}C NMR (75 MHz, CD_3OD): δ: 136.0 (C), 131.2 (CH), 130.7 (CH), 130.4 (CH), 130.2 (CH), 129.4 (CH), 60.8 (CH), 58.1 (CH_2), 55.2 (CH_2), 54.6 (CH), 47.2 (CH_2), 42.0 (CH_2), 40.8 (CH_2), 38.3 (CH_2), 38.0 (CH_2), 37.5 (CH_2), 36.6 (CH_2), 30.7 (CH_2), 27.7 (CH_2), 27.5 (CH_2), 27.7 (CH_2), 26.7(CH_2), 25.5 (CH_2), 19.3 (CH_2), 12.5 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 11.12 min.; % purity >90%; HRMS for $C_{30}H_{55}N_4$ (MH^+) calcd 471.4421 found 471.4425.

4.5.3: Synthesis Of Triazacyclononane 189



189

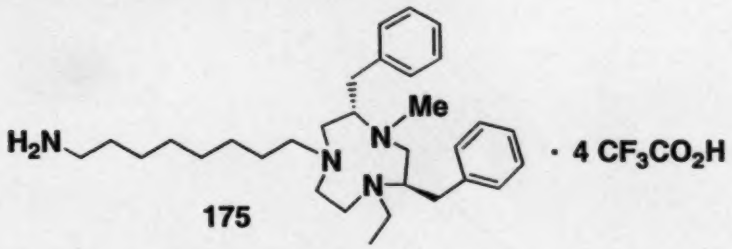
Compound **189** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded **189** as its *tetrakis*(trifluoroacetate) salt, in a 2.5:1 mixture (LC-MS) with its quaternary piperazinium analogue as the minor component, which was purified by semi-preparative HPLC and isolated as its *tetrakis*(trifluoroacetate) salt in 18% overall yield from its corresponding peptide.

^{1}H NMR (500 MHz, CD_3OD): δ: 7.47-7.36 (m, 5H), 4.30-4.20 (m, 2H), 4.09-3.94 (m, 2H), 3.90-3.82 (m, 1H), 3.72-3.66 (m, 3H), 3.44-4.38 (m, 1H), 3.38-3.22 (m, 3H), 3.10-2.94 (m, 4H), 2.94-2.82 (m, 4H), 2.34-2.24 (m, 1H), 2.20-2.10 (m, 1H), 2.10-2.00 (m, 1H), 1.70-1.52 (m, 5H), 1.44-1.26 (m, 13H)

^{13}C NMR (100 MHz, CD_3OD): δ: 133.0 (C), 131.1 (2 x CH), 130.6 (2 × CH), 120.3 (CH), 71.1 (CH), 61.1 (CH_2), 58.0 (2 × CH_2), 55.0 (CH), 54.2 (CH_2), 48.4 (CH_2), 42.1 (CH_2), 40.7 (CH_2), 38.3 (CH_2), 30.1 (CH_2), 30.0, (CH_2), 28.6 (CH_2), 27.8 (CH_2), 27.4 (2 × CH_2), 26.3 (CH_2), 25.6 (CH_2), 19.4 (CH_2), 12.3 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 8.737; % purity > 90%; HRMS for $C_{26}H_{47}N_4$ (MH^+) calcd 415.3795, found 415.3799

4.5.4: Synthesis Of Triazacyclononane 175



175

Compound **175** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded **175** as its *tetrakis*(trifluoroacetate) salt, in a 1:1 mixture with its quaternary piperazinium analogue (LC-MS), which was purified by semi-preparative HPLC and isolated as its *tetrakis*(trifluoroacetate) salt in 23% overall yield from its corresponding peptide.

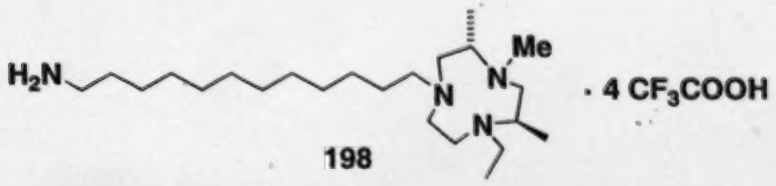
^{1}H NMR (500MHz, CD_3OD): δ: 7.47-7.26 (m, 10H), 4.26-4.08 (m, 3H), 3.98-3.86 (m, 2H), 3.66-3.56 (m, 2H), 3.46-3.32 (m, 3H), 3.02 (dd, 1H, J_1=9.1 Hz, J_2 = 11.2 Hz), 2.98-2.76 (m, 5H), 2.66-2.52 (m, 5H), 1.68-1.56 (m, 3H), 1.44-1.18 (m, 16H)

^{13}C NMR (125 MHz, CD_3OD): δ: 140.0 (C), 139.9 (C), 131.3 (CH), 130.6 (CH), 130.3 (CH), 130.3 (CH), 129.4 (CH), 128.5 (CH), 61.6 (CH), 57.7 (CH_2), 55.6 (CH_2), 46.9 (CH_2), 42.1 (CH_2), 40.7 (CH_2), 38.7 (CH_2), 33.0 (CH_3), 30.2 (2 × CH_2), 30.1 (2 × CH_2), 28.6 (2 × CH_2), 27.8 (CH_2), 27.4 (2 × CH_2), 26.9 (CH_2), 12.6 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD

detector. Rt = 15.54 min; purity > 90%; HRMS for $C_{31}H_{51}N_4$ (MH^+) calcd 479.4108, found 479.4113

4.5.5: Synthesis Of Triazacyclononane 198



198

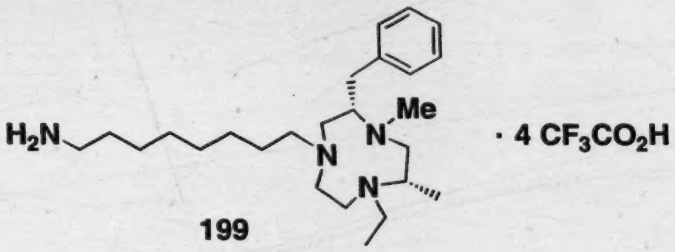
Compound **198** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded **198** as its *tetrakis*(trifluoroacetate) salt in a 6:5 mixture with its quaternary piperazinium analogue (LC-MS) in 78% crude yield.

^{1}H NMR (300 MHz, CD_3OD): δ: 4.26-3.94 (m, 3H), 3.92-3.72 (m, 2H), 3.71-3.52 (m, 2H), 3.52-3.44 (m, 1H), 3.44-3.38 (m, 1H), 3.28-3.08 (m, 6H), 3.08-2.84 (m, 6H), 1.74-1.54 (m, 8H), 1.52-1.26 (m, 21H)

^{13}C NMR (100 MHz, CD_3OD): δ: 72.1 (CH), 68.9 (CH_2), 67.6 (CH), 61.0 (CH_2), 57.9 (CH_2), 53.3 (CH_2), 49.7 (CH_2), 48.4 (CH_2), 41.7 (CH_2), 41.6 (CH_2), 40.8 (CH_3), 30.7 (CH_2), 30.7 (CH_2), 30.5 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 28.6 (CH_2), 28.0 (CH_2), 27.5 (CH_2), 36.7 (CH_2), 18.9 (CH_3), 18.2 (CH_2), 12.6 (CH_3), 11.7 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 9.26 min, % purity > 85%; HRMS: calcd for $C_{23}H_{51}N_4$ (MH^+) 383.4108, found 383.4105

4.5.6: Synthesis Of Triazacyclononane 199



199

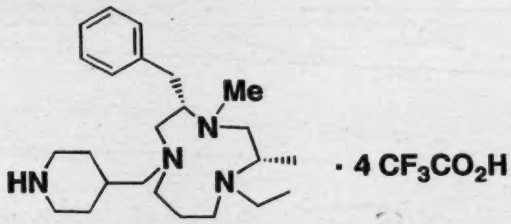
Compound **199** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded **199** as its *tetrakis*(trifluoroacetate) salt, as the minor constituent in a 5:7 mixture with its quaternary piperazinium analogue (LC-MS), which was purified by semi-preparative HPLC and isolated as its *tetrakis*(trifluoroacetate) salt in 17% overall yield from its corresponding peptide.

^{1}H NMR (CD_3OD, 500 MHz): δ: 7.41-7.28 (m, 5H), 4.24-4.14 (m, 2H), 3.93 (dd, 1H, J_1 = 4.6 Hz, J_2 = 10.6 Hz), 3.90-3.42 (m, 2H), 3.60-3.54 (m, 1H), 3.38 (s, 3H), 3.22 (q, 2H, J = 4.9 Hz), 3.14 –3.03 (m, 3H), 2.88 (t, 3H, J = 4.8 Hz), 2.84 –2.78 (m, 2H), 1.68 –1.58 (m, 5H), 1.52-1.44 (m, 2H), 1.42- 1.24 (m, 15H)

^{13}C NMR (CD_3OD, 75 MHz): δ: 135.7 (C), 130.4 (CH), 130.3 (CH), 129.0 (CH), 73.5 (CH), 68.2 (CH_2), 61.5 (CH), 57.8 (CH_2), 51.2 (CH_2), 46.8 (CH_2), 41.8 (CH_2), 40.7 (CH_3), 33.1 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 28.6 (2x CH_2), 27.7 (CH_2), 27.4 (CH_2), 26.5 (CH_2), 23.8 (CH_2), 19.0 (CH_3), 11.7 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 9.048 min., % purity >95 %; HRMS for $C_{25}H_{47}N_4$ (MH^+) calcd 403.3795, found 403.3793.

4.5.7: Synthesis Of Triazacylcodecane 146



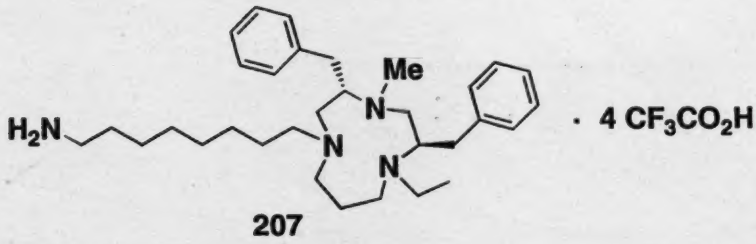
146

Compound **146** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded crude **146** as its *tetrakis*(trifluoroacetate) salt in 94% crude yield.

^{1}H NMR (300 MHz, CD_3OD): δ: 7.50-7.20 (m, 5H), 4.56-3.79 (m, 3H), 2.60-3.40 (m, 5H), 3.25-2.80 (m, 5H), 2.60-2.20 (m, 2H), 2.15-1.78 (m, 2H), 1.70-1.40 (m, 8H), 1.40-1.20 (m, 10H), 1.00-0.80 (m, 1H)

LC-MS: Zorbax SB-C8: eluent: 12.5% MeCN (0.1% TFA) in water (0.1% TFA) over 10 min. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 3.386 min.; % purity = 45%; ES-MS *m/z* $(M + H)^+$ = 387.4; HRMS for $C_{24}H_{43}N_4$ (MH^+) calcd 387.3488 found 387.3482

4.5.8: Synthesis Of Triazacyclodecane 207



207

Compound **207** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded **207** as its *tetrakis*(trifluoroacetate) salt, with little observed formation of its corresponding 7-membered ring quaternary ammonium

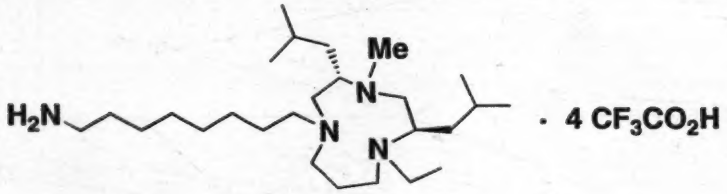
isomer (>10:1), which was purified by semi-preparative HPLC and isolated as its *tetrakis*(trifluoroacetate) salt in 14% overall yield from its corresponding peptide.

^{1}H (500 MHz, CD_3OD): δ: 7.42-7.02 (m, 10 H), 3.48 – 3.34 (m, 2H), 3.28 –3.20 (m, 1H), 3.18-3.10 (m, 1H), 3.10-2.98 (m, 2H), 2.96 – 2.76 (m, 6H), 2.78-2.64 (m, 2H), 2.60-2.42 (m, 3H), 2.40-2.30 (m, 1H), 2.26- 21.0 (m, 3H), 1.82-1.68 (m, 1H), 1.68-1.58 (m, 3H), 1.46-1.14 (m, 17H)

^{13}C NMR (125 MHz, CD_3OD): δ: 139.9 (C), 139.1 (C), 130.8 (CH), 130.2 (CH), 129.8 (CH), 129.7 (CH), 127.8 (CH), 127.6 (CH), 65.0 (CH), 61.1 (CH_2), 59.8 (CH), 58.0 (CH_2), 54.6 (CH_2), 54.2 (CH_2), 48.3 (CH_2), 43.5 (CH_3), 36.3 (CH_2), 32.1 (CH_2), 31.6 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 28.6 ($2 \times CH_2$), 28.2 (CH_2), 28.0 (CH_2), 27.4 ($2 \times CH_2$), 25.6 (CH_2), 21.1 (CH_2), 12.6 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt= 13.879, % purity > 90 %; HRMS for $C_{32}H_{53}N_4$ (MH^+) calcd 493.4265 found 493.4268

4.5.9: Synthesis Of Triazacyclodecane 202

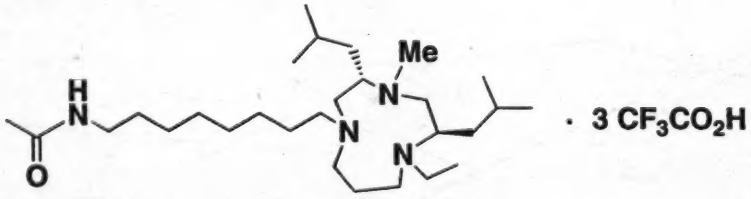


202

Compound **202** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded **202** as its *tetrakis*(trifluoroacetate) salt, in a 7:2 ratio with its corresponding 7 member-ring quaternary ammonium analogues, which was not purified by semi-preparative HPLC but rather was acetylated and purified at that stage (see preparation of **204** for details).

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 13.044 min; ES-MS *m/z* $(M + H)^+ = 425.5$

4.5.10: Acetylation Of 202 To 204:



204

0.24g of crude **202** (0.27 mmol, *tetrakis*(trifluoroacetate) salt) was placed in a round-bottom flask (equipped with a stir bar) and dissolved in 2ml of DMF. To this was added 0.2 ml of NEt_3 (101.2 $gmol^{-1}$, 0.726 gml^{-1}, 0.15g, 1.43 mmol) followed by 0.5 ml of acetic anhydride (102.1 gml^{-1}, 1.082 gml^{-1}, 0.54 g, 5.3 mmol). The solution was stirred for 6h at which time the suspension was evaporated to dryness. The sample was further dried under vacuum for 24h following which the sample was analyzed using the general

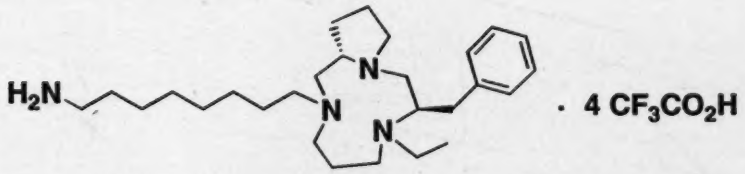
HPLC conditions and then purified using semi-preparative HPLC which afforded **204** as its *tris*(trifluoroacetate)salt in 20% overall yield from its corresponding peptide.

^{1}H NMR (500 MHz, CD_3OD): δ: 3.60-3.68 (m, 2H), 3.30-3.20 (m, 2H), 3.20-3.10 (m, 5H), 3.05-2.95 (m, 2H), 1.90-2.79 (m, 2H), 2.75-2.60 (m, 2H), 2.43-2.35 (m, 1H), 2.34-2.20 (m, 4H), 1.92 (s, 3H), 1.84-1.78 (m, 1H), 1.75-.165 (m, 1H), 1.68-1.54 (m, 4H), 1.52-1.48 (m, 4H), 1.40-1.30 (m, 10H), 1.30-1.20 (m, 3H), 1.10-0.90 (m, 12H)

^{13}C NMR (100 MHz, CD_3OD): δ: 78.2 (C), 67.1 (CH_2), 59.8 (CH_2), 58.8 (CH_2), 57.6 (CH_2), 56.9 (CH), 56.1 (CH), 53.5 (CH_2), 52.5 (CH_2), 48.7 (CH_2), 44.3 (CH_2), 39.2 (CH_2), 38.4 (CH_2), 33.1 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 25.5 (CH_3), 25.3 (CH_3), 23.0 (CH_3), 22.6 (CH_3), 24.4 (CH_2), 21.3 (CH_3), 19.8 (CH_2), 18.1 (CH_2), 11.2 (CH_3), 11.0 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 16.146 min, purity > 99%; HRMS for $C_{28}H_{59}N_4O$ (MH^+) calcd 467.4683 found 467.4685

4.5.11: Synthesis Of Triazacyclodecane 210



210

Compound **210** was prepared according to general procedure 4.1.5. Cleavage of the resin with 5% TFA/CH_2Cl_2 afforded **210** as an oil of its *tetrakis*(trifluoroacetate) salt, in a 9:1 ratio with its 7-member-ring quaternary ammonium analogues as the minor component, which was purified by semi-preparative HPLC and isolated as its *tetrakis*(trifluoroacetate) salt in 17% overall yield from its corresponding peptide.

^{1}H (500 MHz, CD_3OD): δ: 7.35-7.22 (m, 5H), 3.74-3.60 (m, 2H), 3.46-3.32 (m, 3H), 3.18 (3.04 (m, 3H), 3.40-2.94 (m, 2H), 2.92-2.84 (m, 4H), 2.62-2.54 (m, 1H), 2.52-2.40 (m,

1H), 2.36-2.24 (m, 1H), 2.28-2.08 (m, 1H), 1.92-1.78 (m, 2H), 1.78-1.68 (m, 1H), 1.68-1.46 (m, 4H), 1.42-1.24 (m, 18H)

^{13}C NMR (75 MHz, CD_3OD): δ: 138.0 (C), 130.1 (CH), 130.0 (CH), 128.1 (CH), 65.5 (CH), 65.6 (CH_2), 59.9 (CH), 58.0 (CH_2), 55.3 (CH_2), 53.4 (CH_2), 40.7 (CH_2), 31.8 (CH_2), 30.3 (2 × CH_2), 30.1 (2 × CH_2), 30.0 (2 × CH_2), 28.5 (CH_2), 27.8 (CH_2), 27.3 (CH_2), 25.4 (CH_2), 24.3 (CH_2), 21.4 (CH_2), 12.0 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 11.550, purity > 99%; HRMS for $C_{27}H_{49}N_4$ (MH^+) calcd 429.3952, found 429.3952

4.6: Epoxidation Studies

4.6.1: Epoxidation Of Styrene Attempts Using Resin-Bound Ligand 149

The epoxidation protocol was analogous to the general procedure described in section 4.1.6.1 except that the metal source, solvent, temperature, and additive were varied as described in Table 3.1. In all cases, no epoxidation of styrene was observed.

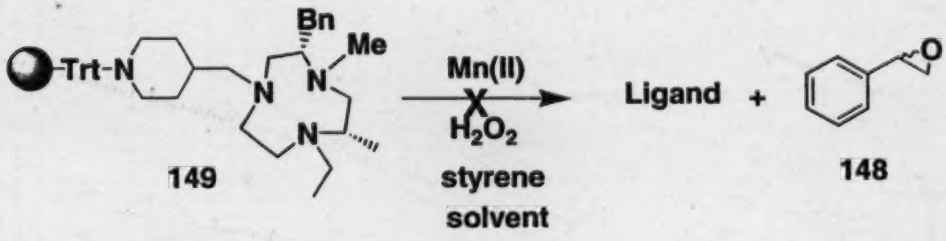


Table 3.1:

Conditions*	Metal Source	Result
Styrene, H_2O_2, THF:H_2O 1:1, 0 °C, Na-L-ascorbate	$Mn(OAc)_2.4H_2O$	No epoxidation
Styrene, H_2O_2, THF:H_2O 1:1, Na-L-ascorbate Room Temperature	$Mn(OAc)_2.4H_2O$	No epoxidation
Styrene, H_2O_2, DCM:H_2O 2:1, Room Temperature	$Mn(OAc)_2.4H_2O$	No epoxidation
Styrene, H_2O_2, THF:MeOH 1:1, Na-L-ascorbate Room Temperature	$MnCl_2.4H_2O$	No epoxidation
Styrene, H_2O_2, THF:MeCN 1:1, Na-L-ascorbate Room Temperature	$MnCl_2.4H_2O$	No epoxidation

*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 µL; Ligand:metal: = 1.7:1 = 25 µmol: 15 µmol

4.6.2: Epoxidation Of Styrene Attempts Using Resin Bound Ligand 154:

The epoxidation of styrene experiments were conducted as described in section 4.1.6.1 except that the metal source, additive, and solvent were varied. No epoxidation was observed. The results for these experiments are summarized in Table 3.2.

Table 3.2:

Conditions*	Metal source	Result
Binding study:THF:H_2O (2:1)	$MnCl_2 \cdot 4H_2O$	$Mn(NH_4)PO_4$ precipitate observed
Epoxidation study: MeCN:THF (1:1) Na-L-ascorbate H_2O_2	$MnCl_2 \cdot 4H_2O$	Little epoxide observed
Binding study: THF:MeOH (1:1) 72h	$MnCl_2 \cdot 4H_2O$	Little $Mn(NH_4)PO_4$ precipitate observed
Binding study: THF: MeOH (1: 1) 72 h	$Mn(OAc)_2 \cdot 4H_2O$	Little $Mn(NH_4)PO_4$ precipitate observed

*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 µL; Ligand:metal: = 1.7:1 = 25 µmol: 15 µmol

4.6.3: Epoxidation Of Styrene Attempts Using Resin Bound Ligand 161:

The epoxidation of styrene experiments were conducted as described in section 4.1.6.1 except that the metal source, additive, and solvent were varied. Essentially no epoxidation was observed. The results for these experiments are summarized in Table 3.3.

Table 3.3:

Conditions*	Metal source	Result
Acetone:THF:H_2O (1:1:1)	$MnCl_2 \cdot 4H_2O$	No Epoxide
THF:H_2O (1:1) Na-L-ascorbate H_2O_2	$MnCl_2 \cdot 4H_2O$	Little epoxide observed
Acetone:THF:H_2O (1:1:1)	$Mn(OAc)_2 \cdot 4H_2O$	No epoxide
THF: H_2O (1: 1) Na-L-ascorbate	$Mn(OAc)_2 \cdot 4H_2O$	No epoxide

*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 µL; Ligand:metal: = 1.7:1 = 25 µmol: 15 µmol

4.6.4: Epoxidation Attempts With Ligands 167, 168 and 169

The epoxidation of styrene experiments were conducted as described in section 4.1.6.2 except that the metal source, temperature, additive, and solvent were varied. No epoxidation was observed. The results are summarized in Table 3.4.

Table 3.4:

Compound*	Conditions	Result
(a) **169**	Styrene/Acetone/0 °C/Na-oxalate-oxalic acid/ $Mn(OAc)_2 \cdot 4H_2O/H_2O_2$	No epoxidation observed
(b) **167**	Styrene/1:1 acetone:DCM/ 0 °C/ Na-oxalate-oxalic acid/ $Mn(OAc)_2 \cdot 4H_2O/H_2O_2$	No epoxidation observed
(c) **168**	Styrene/0 °C/acetone/$Mn(OAc)_2 \cdot 4H_20$/ NEt_3/H_2O_2	No epoxidation observed
(d) **168**	Styrene/0 °C/acetone/$Mn(OAc)_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid/ H_2O_2	No epoxidation observed

*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 μL; Ligand:metal: = 1.7:1 = 25 μmol: 15 μmol

4.6.5: Epoxidation Of Styrene Attempts With Ligands 170, 171, and 172

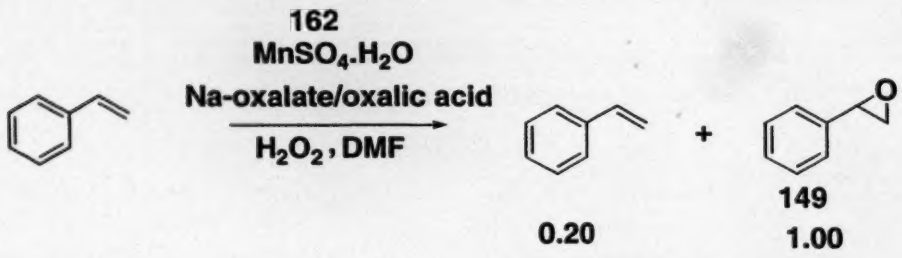
The epoxidation of styrene experiments were conducted as described in section 4.1.6.1 and 4.1.6.2 except that the metal source, temperature, additive, and solvent were varied in some cases. Epoxidation was observed in the carbonate-bicarbonate buffer system, which was due to these buffer conditions rather than the ligand. The results of these studies are summarized below.

Table 3.5:

Compound*	Conditions	Result
(a) **170**	Styrene/ $MnCl_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid/MeCN/ 0 °C/NEt_3/H_2O_2	No epoxidation
(b) **170**	Styrene/ $MnCl_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid/ MeCN/ 0 °C/H_2O_2	No epoxidation
(c) **170**	Styrene/CH_2Cl_2/$MnCl_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid / 50 °C/H_2O_2	No epoxidation
(d) **170**	Styrene/$MnSO_4 \cdot H_2O$/Na_2CO_3-$NaHCO_3$(pH≅ 8.0)/DMF/ H_2O_2	Ratio of styrene:styrene oxide = 1:0.7
(e) **171**	Styrene/$MnSO_4 \cdot H_2O$/Na_2CO_3-$NaHCO_3$(pH≅ 8.0)/DMF/ /H_2O_2	Ratio of styrene:styrene oxide = 0.38:1.00
(f) **172**	Styrene/acetone/$MnCl_2 \cdot 4H_2O$/ Na-oxalate-oxalic acid/0 °C/H_2O_2	No epoxidation

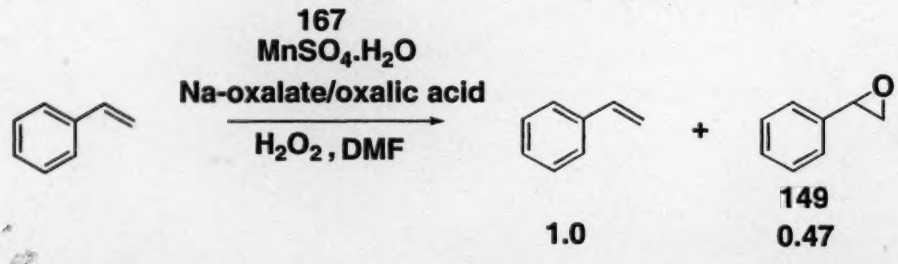
*Note: styrene = 0.67 mmol, 0.909 gml^{-1}, 77 μL; Ligand:metal: = 1.7:1 = 25 μmol: 15 μmol

4.6.6: Epoxidation Of Styrene Attempts With Resin Bound Ligand 162



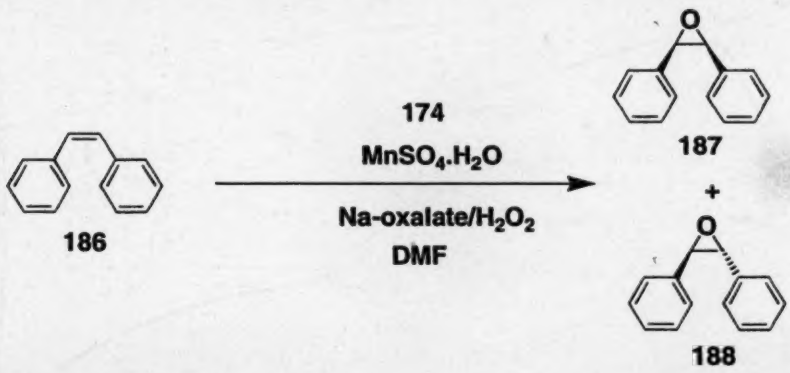
The epoxidation of styrene experiments were conducted as described in section 4.1.6.1. The ratio of styrene:styrene oxide was determined to be 0.20: 1.00 by ^{1}H NMR spectroscopy.

4.6.7: Epoxidation Of Styrene Attempts With Resin Bound Ligand 167



The epoxidation of styrene experiments were conducted as described in section 4.1.6.1. The ratio of styrene to styrene oxide was determined to be 1.0:0.47 by ^{1}H NMR spectroscopy.

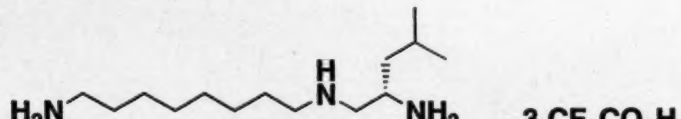
4.6.8: Epoxidation Of *cis*-Stilbene With Resin Bound Ligand 174



The epoxidation of *cis*-stilbene was conducted as described in section 4.1.6.1 for styrene epoxidation. The ratio of *cis*-stilbene oxide to *trans*-stilbene oxide was determined to be 1:2 by ^{1}H NMR spectroscopy. The ratio of starting material to product was determined to be 1:0.2.

4.7: Richman-Atkins Approach

4.7.1: Synthesis Of Triamine 218b



218b

To 0.50 g of resin **86** (1.13 mmol/g), suspended in DMF in a PP vessel, was added 4 equiv. of HOBt, 4 equiv. Fmoc-L-Leu-OH, and 8 equiv. of DIPEA. The resulting suspension was placed on a shaker for 3 h at which point the resin was filtered and washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin colorometric assay was negative.[51] The resin was again washed with 3 × DMF and then treated with a 20% piperidine/DMF solution, with shaking on an agitator, for 45 minutes. The solution was once again drained and the resin washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin colorometric assay was positive.[51] The resulting amide was transferred to a round bottom flask equipped with a condenser and stir bar and suspended in a minimum

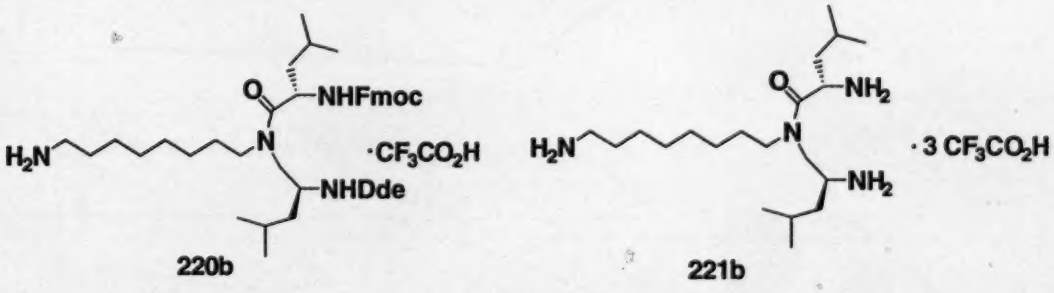
amount of THF. The resin was then treated with 40 equiv. of a 1 M BH_3·THF solution and stirred for 24 h at 65 °C. The resin was then filtered into a PP vessel and washed with 3 × THF. To the PP vessel was then added 25 equiv. of I_2 as a concentrated THF solution along with 4 ml/g resin of acetic acid and 2 ml/g resin of DIPEA. The resulting dark suspension was shaken on an agitator for 4 h. The solution was drained and washed with 3 × THF, 3 × Et_3N/DMF (1:3), 3 × MeOH, and 3 × CH_2Cl_2, giving resin **218b**. The resin was then dried *in vacuo* for > 12 h. Cleavage of a small sample of the resin with 5% TFA/CH_2Cl_2 provided compound **218b** as its *tris*(trifluoroacetate) salt in 83 % yield.

^{1}H NMR (400 MHz, CD_3OD): δ: 3.67-3.58 (m, 1H), 3.12-2.99 (m, 2H), 2.92-2.84 (m, 4H), 1.78-1.52 (m, 6H), 1.42-1.30 (m, 2H), 1.00-0.90 (m, 6H)

^{13}C NMR (75 MHz, CD_3OD): δ: 50.9 (CH_2), 50.0 (CH_2), 48.5 (CH), 41.15 (CH_2), 40.7(CH_2), 30.0 (CH_2), 29.9 (CH_2), 28.5 (CH_2), 27.3 (CH_2), 27.1 (CH_2), 25.2 (CH), 22.65 (CH_3), 22.2 (CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 5.86 min. % purity > 85%; HRMS for $C_{14}H_{34}N_3$ (MH^+) calcd 244.2747 found 244.2743

4.7.2: Synthesis Of Protected Amide 220b And Amide 221b



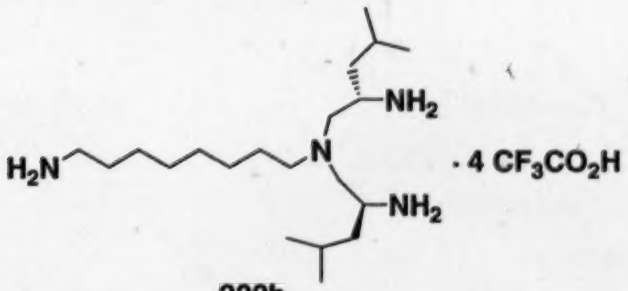
Resin **218b** from above was transferred to a PP vessel and suspended in DMF. The resin was then treated with 2 equiv. (based on resin loading) of 2-acetyldimedone in DMF for 24 h. The resin was then drained and washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. A ninhydrin colorimetric assay was negative.[51] The resin was then subjected

to a second round of peptide coupling by suspending the resin in DMF and adding to the resin 3 equiv. of Fmoc-L-Leu-OH, 3 equiv. of HATU, and 6 equiv. of DIPEA. The resulting suspension was placed on a shaker for 4 hours. The resulting resin was drained and washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2 to give the di-protected amide **220b** as its trifluoroacetate salt in > 95% purity and 90% yield, as confirmed by LC-MS. This resin was then rinsed with 3 × DMF and then was treated with a 2% hydrazine/DMF solution for 45 minutes, followed by a DMF rinses, and then a 20% piperidine/DMF solution for 45 minutes. The resin was washed with 3 × DMF, 3 × MeOH, and 3 × CH_2Cl_2. The resin was dried in vacuo for > 12 h to give amide **221b** as its *tris*(trifluoroacetate) salt in > 95 % purity and 90 % yield, as confirmed by LC-MS.

LC-MS for **220b**: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 17.727 min. % purity > 95%

LC-MS for **221b**: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 9.665 min. % purity > 95%

4.7.3: Synthesis Of Branched Tetramine 222b



222b

Resin **221b** was transferred to a round bottom flask equipped with a condenser, stir bar, and N_2 inlet. The polymer was suspended in a minimum amount of THF and then treated with 40 equiv. (based on resin loading) of a 1 M BH_3·THF solution, 12 equiv. $B(OMe)_3$, and 12 equiv. of $B(OH)_3$ for 24 h at 65°C. The resin was transferred to

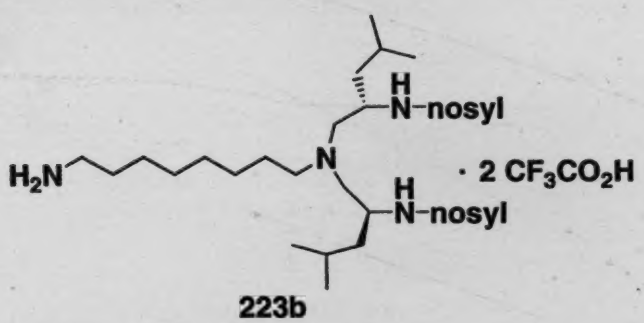
a PP vessel and washed with THF (3×) and the suspended in THF. The resin was once again transferred into a round bottom flask equipped with a condenser, stir bar and N_2 inlet. The resin was then treated with 10 ml of piperidine and stirred at 65°C for 24 h. The resulting suspension was drained and washed with MeOH (3×), and CH_2Cl_2 (3×). The resulting branched tetramine **222b** was dried *in vacuo* for > 12 h. Cleavage of a small sample of the resin with 5% TFA/CH_2Cl_2 provided tetramine **222b** as its *tetrakis*(trifluoroacetate) salt in > 85% purity, and > 83% yield as confirmed by LC-MS.

^{1}H NMR (500 MHz, CD_3OD): δ: 3.35-3.30 (m, 3H), 2.94-2.86 (m, 5H), 2.64-2.56 (m, 1H), 2.52-2.46 (m, 1H), 1.80-1.72 (m, 2H), 1.68-1.60 (m, 5H), 1.42-1.44 (m, 3H), 1.42-1.28 (m, 12H), 1.02-0.92 (m, 8H)

^{13}C NMR (75 MHz, CD_3OD): δ: 58.9 (CH_2), 54.7 (CH), 53.5 (CH_2), 52.0 (CH), 41.3 (CH_2), 40.7 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 30.0 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 27.4 (CH_2), 27.4 (CH_2), 25.6 (CH), 22.8 (2 × CH_3), 22.7 (2 × CH_3)

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 9.595 min. % purity > 85%; HRMS for $C_{20}H_{47}N_4$ (MH^+) cald 343.3795 found 343.3790

4.7.4: Synthesis Of Nosyl-Protected Tetramine 223b



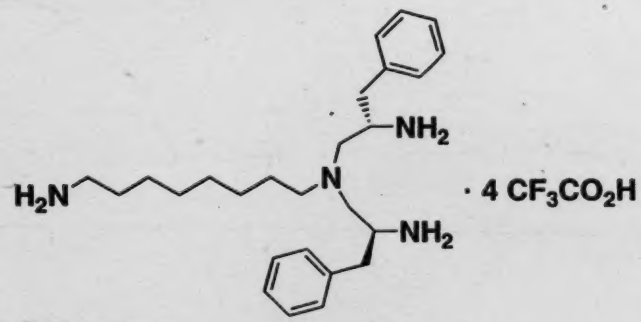
223b

To resin **222b** in a PP vessel (from above), swollen in CH_2Cl_2, was added 8 equiv. of 2-nitrobenzenesulfonyl chloride and 70 equiv. of Et_3N. The resulting suspension was placed on a shaker for 4 h at which point it was drained and washed with CH_2Cl_2 (3×),

MeOH (3×), and finally CH_2Cl_2 (3×). The resin was dried *in vacuo* for > 12 h. Cleavage of a small sample of the resin with 5% TFA/CH_2Cl_2 provided **223b** as its *bis*(trifluoroacetate) salt in 80% yield.

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 15.315 min.; % purity > 85%; HRMS for $C_{32}H_{52}N_6O_8S_2$ (MH^+) cald 713.33608 found 713.33636

4.7.5: Synthesis Of Tetramine 222a

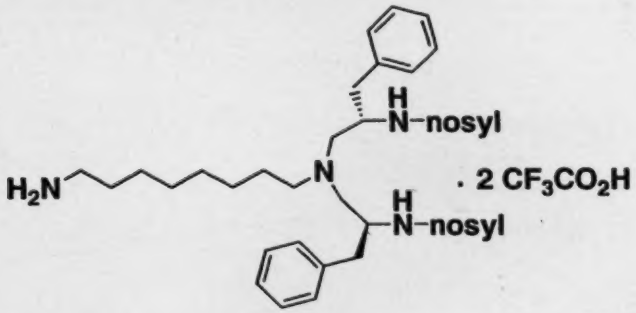


222a

Resin **222a** was prepared exactly as described above. Cleavage of a small sample of this resin with 5% TFA/CH_2Cl_2 gave **222a** as its *tetrakis*(trifluoroacetate) salt in 75 % crude yield.

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 11.064 min.; % purity > 51%; HRMS for $C_{26}H_{43}N_4$ (MH^+) calcd 411.3482 found 411.3485

4.7.6: Synthesis Of Nosyl-Protected Tetramine 223a

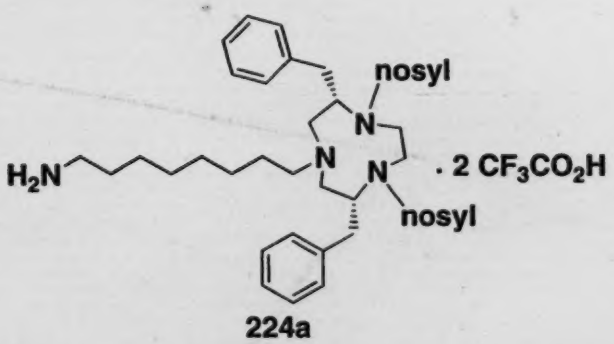


223a

Di-protected amine **223a** was prepared as described above. Cleavage of a small sample of the resin with 5% TFA/CH_2Cl_2 gave **223a** as its *bis*(trifluoroacetate) salt in 85% yield.

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 15.395 min.; % purity = 70%

4.7.7: Synthesis Of Triazacyclononane 224a



224a

To resin **223a,** suspended in DMF in a round bottom flask, was added 15 equiv. of cesium carbonate followed by 12 equiv. of the bis-tosylate of ethylene glycol. The suspension was heated to 50°C and left overnight. The resin was transferred to a PP vessel and rinsed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×). Cleavage of a small

sample of the resin with 5% TFA/CH_2Cl_2 gave triazacyclononane **224a** as a *bis*(trifluoroacetate) salt in a complex mixture, as confirmed by LC-MS. Subsequent attempts at cyclization have so far met with failure.

LC-MS: Zorbax SB-C8: eluent: 2-50% MeCN (0.1% TFA) in water (0.1% TFA) over 12 min. maintained at 50% for 8 more minutes. Flow rate: 0.7 ml/min. DAD and MSD detector. Rt = 18.357 min. % purity = 35%

Bibliography:

(1) Cohen, S. S. *A Guide to the Polyamines*; Oxford University Press: New York, 1998.

(2) Rosenthal, S. M.; Tabor, C. W. *J. Pharmacol. Exp. Ther.* **1956**, *116*, 131.

(3) Tabor, H.; Tabor, C.W. *Pharmacol. Rev.* **1964**, *16*, 245.

(4) Renault, J.; Lebranchu, M.; Lecat, A.; Uriac, P. *Tetrahedron Lett.* **2001**, *42*, 6655-6658.

(5) Fischer, F. G.; Bohn, H. *Justus Liebigs Ann. Chem.* **1957**, *603*, 232-249.

(6) Casero Jr., R. A.; Woster, P. M. *J. Med. Chem.* **2001**, *44*, 1-26.

(7) Karigiannis, G.; Papaioannou, D. *Eur. J. Org. Chem.* **2000**, 1841-1863.

(8) Kuska, V.; Buchan, R.; Thoo Lin, P. K. *Synthesis* **2000**, 1189-1207.

(9) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Tetrahedron* **1992**, *48*, 4475-4515.

(10) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.

(11) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron* **1999**, *55*, 335-344.

(12) Hall, D. G.; Laplante, C.; Manku, S.; Nagendran, J. *J. Org. Chem.* **1999**, *64*, 698-699.

(13) Voet, D.; Voet, J. G.; Pratt, C. W. *Fundamentals of Biochemistry*; John Wiley & Sons, Inc.:, 1999.

(14) Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268-2270.

(15) McMurry, T. J.; Raymond, K. N.; Smith, P. H. *Science* **1989**, *244*, 938-943.

(16) Hori, K.; Haruna, Y.; Kamimura, A.; Tsukube, H.; Inoue, T. *Tetrahedron* **1993**, *49*, 3959-3970.

(17) Thummel, R. P. *Tetrahedron* **1991**, *47*, 6851-6886.

(18) Tsukube, H.; Yamashita, K.; Iwachido, T.; Zenki, M. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1661-1665.

(19) Amin, S.; Morrow, J. R.; Lake, C. H.; Churchill, M. R. *Angew. Chem. Int. Ed.* **1994**, *33*, 773-775.

(20) Bencini, A.; Bianchi, A.; Garcia-Espana, E.; Scott, E. C.; Morales, L.; Wang, B.; Deffo, T.; Takusagawa, F.; Mertes, M. P.; Mertes, K. B.; Paoletti, P. *Bioorg. Chem.* **1992**, *20*, 8-29.

(21) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659-663.

(22) Hage, R.; Iburg, J. E.; Kerschner, J.; Koek, J. H.; Lempers, E. L. M.; Martens, R. J.; Racherla, U. S.; Russel, S. W.; Swarthoff, T.; van Vliet, M. R. P.; Warnaar, J. B.; van der Wolf, L.; Krijnen, B. *Nature* **1994**, *369*, 637.

(23) DeVos, D. E.; Bein, T. *Chem. Commun.* **1996**, 917-918.

(24) DeVos, D. E.; Bein, T. *J. Organometall. Chem.* **1996**, *520*, 195-200.

(25) DeVos, D. E.; Meinershagen, J. L.; Bein, T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2211-2213.

(26) Pulacchini, S.; Shastri, K.; Dixon, N. C.; Watkinson, M. *Synthesis* **2001**, 2381-2383.

(27) Pulacchini, S.; Watkinson, M. *Eur. J. Org. Chem.* **2001**, 4233-4238.

(28) Young, M. J.; Chin, J. *J. Am. Chem. Soc.* **1995**, *117*, 10577-10578.

(29) Rossi, P.; Felluga, F.; Tecilla, P.; Formaggiom, F.; Crisma, M.; Toniolo, C.; Scrimin, P. *J. Am. Chem. Soc.* **1999**, *121*, 6948-6949.

(30) Sissi, C.; Rossi, P.; Felluga, F.; Formaggio, R.; Palumbo, M.; Tecilla, P.; Toniolo, C.; Scrimin, P. *J. Am. Chem. Soc.* **2001**, *123*, 3169-3170.

(31) Wainwright, K. P. *Coord. Chem. Rev.* **1997**, *166*, 35-90.

(32) Warden, A.; Graham B; Hearn, M. T. W.; Spiccia, L. *Org. Lett.* **2001**, *3*, 2855-2858.

(33) Koyama, H.; Yoshino, T. *Bull. Chem. Soc. Jap.* **1972**, *45*, 481.

(34) Searle, G. H.; Geue, R. J. *Aust. J. Chem.* **1984**, *37*, 959-970.

(35) Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230-4234.

(36) Vriesema, B. K.; Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 110-113.

(37) Hoye, R. C.; Richman, J. E.; Dantas, G. A.; Lightbourne, M. F.; Shinneman, L. S. *J. Org. Chem.* **2001**, *66*, 2722-2725.

(38) Kim, B. M.; So, M. S. *Tetrahedron Lett.* **1999**, *40*, 7687-7690.

(39) Kim, B. M.; So, M. S.; Choi, J. H. *Org. Lett.* **2002**, *4*, 949-952.

(40) DeVos, D. E.; de Wildeman, S.; Sels, B. F.; Grobet, P. J.; Jacobs, P. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 980-983.

(41) Rao, Y. V. S.; DeVos, D. E.; Bein, T.; Jacobs, P. A. *Chem.Commun.* **1997**, 355-356.

(42) Grenz, A.; Ceccarellin, S.; Bolm, C. *Chem.Commun.* **2001**, 1726-1727.

(43) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18-29.

(44) Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158-165.

(45) Bodsgard, B. R.; Burstyn, J. N. *Chem.Commun.* **2001**, 647-648.;

(46) Daly, A. M.; Renehan, M. F.; Gilheany, D. G. *Org. Lett.* **2001**, *3*, 663-666.; and references within, especially reference (2).

(47) Deber, C. M.; Torchia, D. A.; Blout, E. R. *J. Am. Chem. Soc.* **1971**, *93*, 4893-4897.

(48) Bycroft, B.; Chan, W. C.; Chhabra, S. R.; Hone, N. D. *J. Chem. Soc. Chem. Commun.* **1993**, 778-779.

(49) Bycroft, B.; Chan, W. C.; Chhabra, S. R.; Kellam, B. *Tetrahedron Lett.* **1997**, *38*, 5391-5394.

(50) Chhabra, S. R.; Hothi, B.; Evans, D. J.; White, P. D.; Bycroft, B.; Chan, W. C. *Tetrahedron Lett.* **1998**, *39*, 1603-1606.

(51) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal.Biochem.* **1970**, *34*, 595-598.

(52) Vaino, A. R.; Janda, K. D. *J. Comb. Chem.* **2000**, *2*, 579-596.

(53) Yan, B. *Combinatorial Chemsitry and High Throughput Screening* **1998**, *1*, 215-229.

(54) Konig, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788-798.

(55) Dourtoglou, V.; Ziegler, J. C.; Gross, B. *Tetrahedron Lett.* **1978**, 1269-1272.

(56) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397-4398.

(57) Angell, Y. M.; Garcia-Echeverria, C.; Rich, D. H. *Tetrahedron Lett.* **1994**, *35*, 5981-5984.

(58) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243-2266.

(59) Lane, C. F. *Aldrichimca Acta* **1973**, *6*, 51.

(60) Hutchins, R. O.; Learn, K.; Nazer, B.; Pytlewski, D. *Org. Prep. Proc. Int.* **1984**, *16*, 335.

(61) Carboni, B.; Monnier, L. *Tetrahedron* **1999**, *55*, 1197-1248.

(62) Murphy, M.M.; Armstrong, R.W.; Ouyang, X. *J. Org. Chem.* **1998**, *63*, 1027-1032.

(63) Manku, S.; Laplante, C.; Kopac, D.; Chan, T.; Hall, D. G. *J. Org. Chem.* **2001**, *66*, 874-885.

(64) Freidinger, R. M.; Hinkle, J. S.; Perlow, D. S.; Arison, B. H. *J. Org. Chem.* **1983**, *48*, 77-81.

(65) Nefzi, A.; Giulianotti, M. A.; Houghten, R. A. *Tetrahedron* **2000**, *56*, 3319-3326.

(66) Salomon, M. F.; Salomon, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 4290-4299.

(67) Vogel, A. I. *Vogel's Qualitative Inorganic Analysis*; 6th ed.; John Wiley & Sons, Inc.: New York, 1987.

(68) DeVos, D. E.; Sels, B. F.; Reynaers, M.; Rao, Y. V. S.; Jacobs, P. A. *Tetrahedron Lett.* **1998**, *39*, 3221-3224.

(69) Lane, B. S.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 2933-2934.

(70) Kopac, D.; Hall, D. G. *J. Comb. Chem.* **2002**, in press.

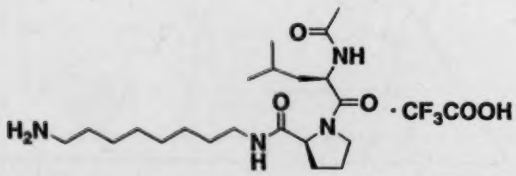
(71) Fukuyama, T.; Cheung, M.; Jow, C. K. *Tetrahedron Lett.* **1995**, *36*, 6373-6374.

(72) Fukuyama, T.; Cheung, M.; Jow, C. K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831-5834.

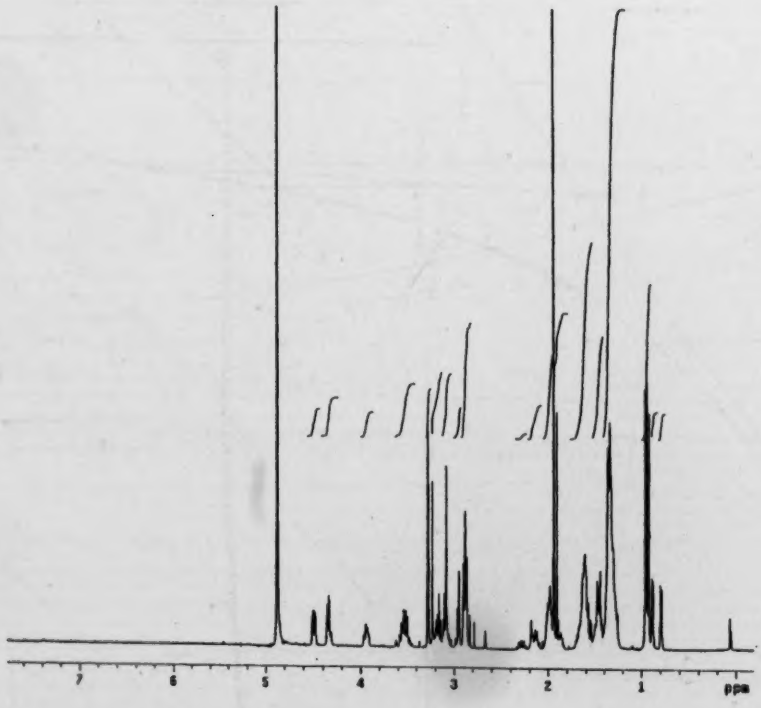
(73) An, H.; Cummins, L. L.; Griffey, R. H.; Bharadwaj, R.; Haly, B. D.; Fraser, A. S.; Wilson-Lingardo, L.; Risen, L. M.; Wyatt, J. R.; Cook, P. D. *J. Am. Chem. Soc.* **1997**, *119*, 3696.

APPENDIX OF SELECTED SPECTRA

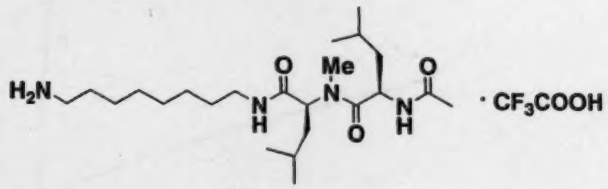
500 MHz ^{1}H NMR in CD_3OD



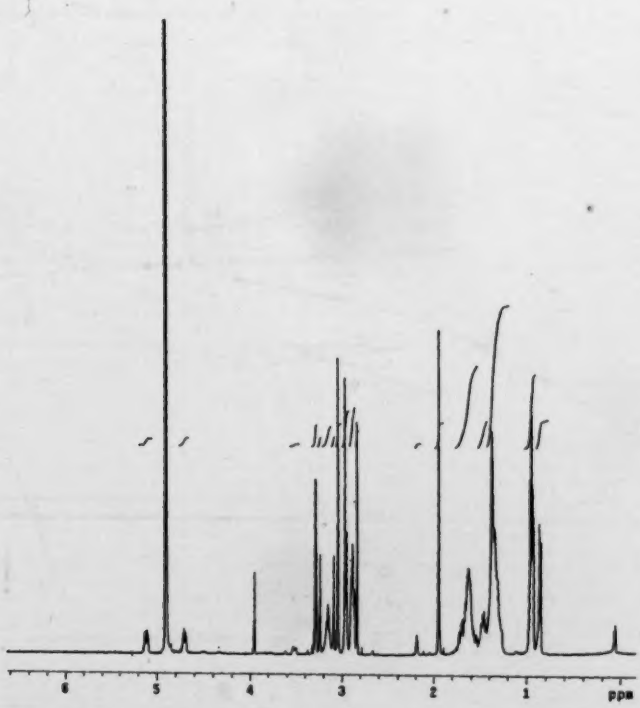
134f



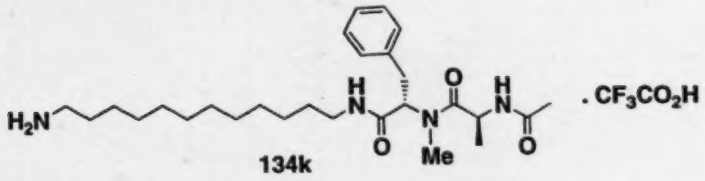
500 MHz ^{1}H NMR in CD_3OD



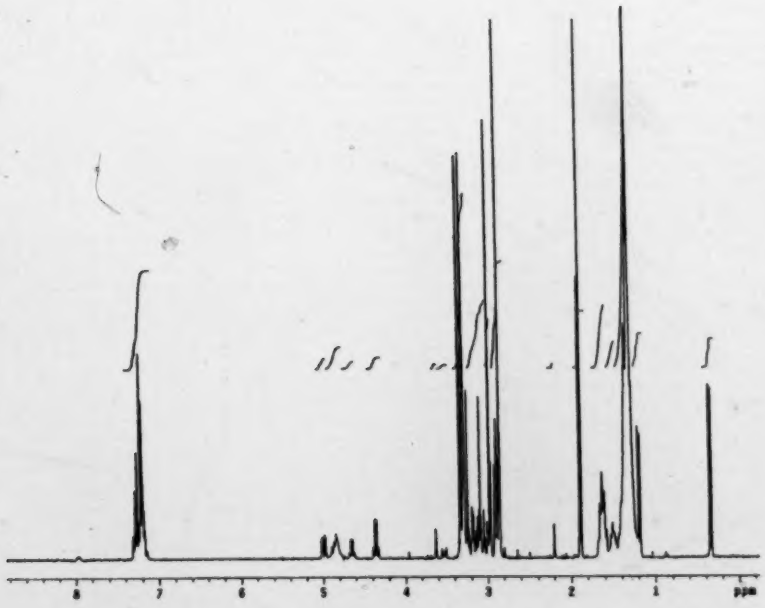
134g



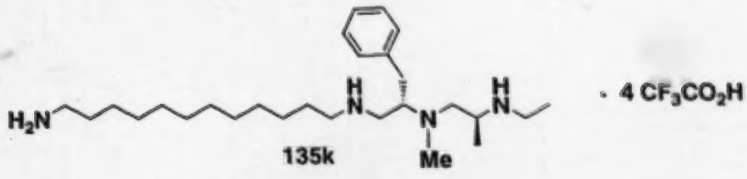
500 MHz ^{1}H NMR in CD_3OD

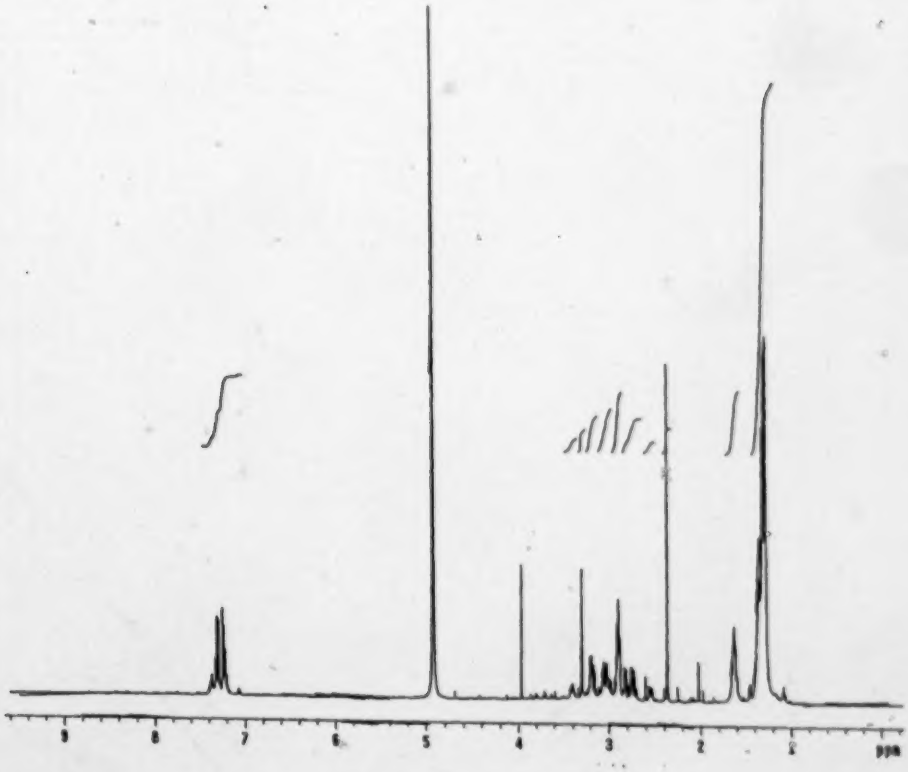


134k

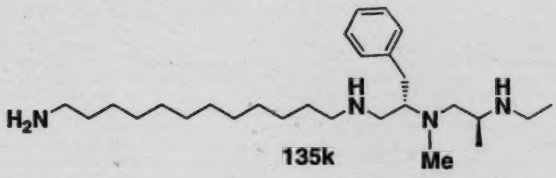


500 MHz ^{1}H NMR in CD_3OD

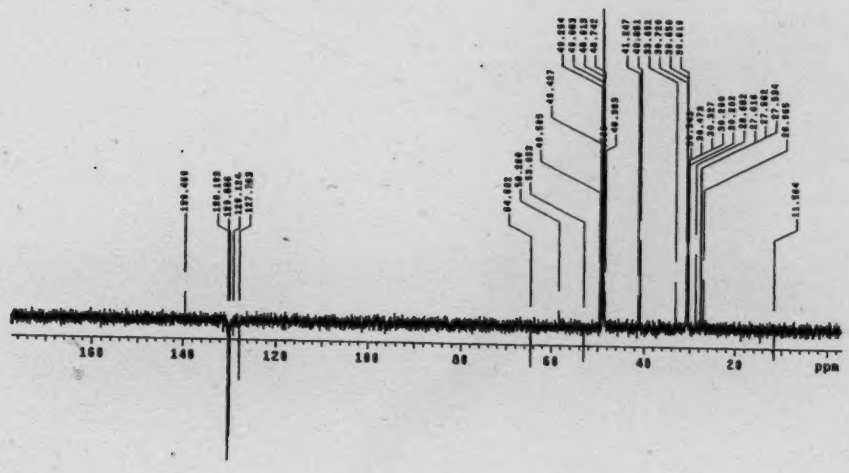




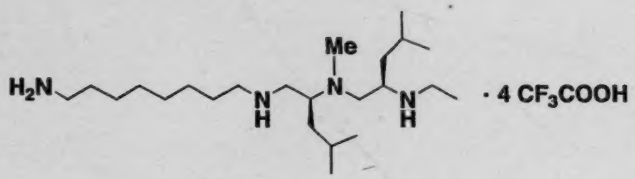
125 MHz ^{13}C NMR in CD_3OD



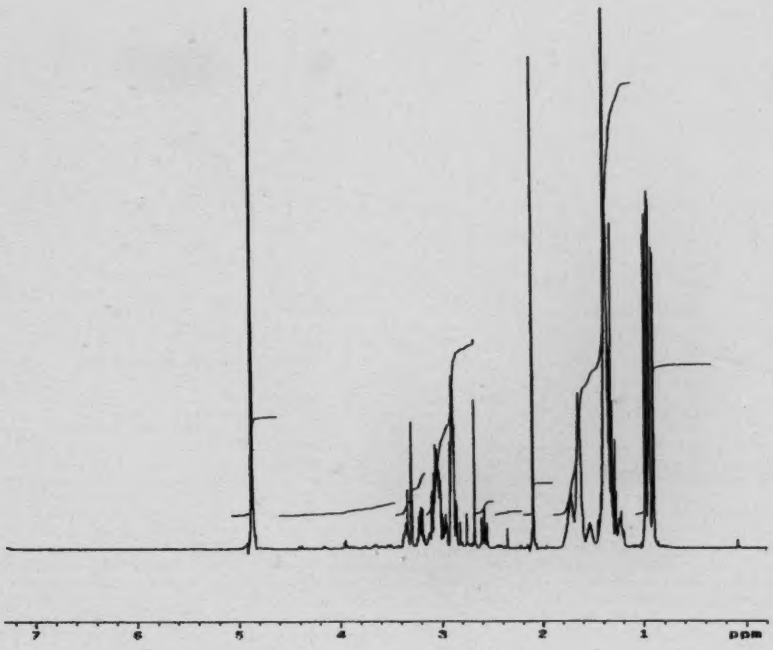
· 4 CF_3CO_2H



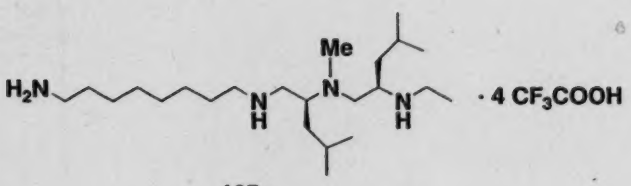
300 MHz ^{1}H NMR in CD_3OD



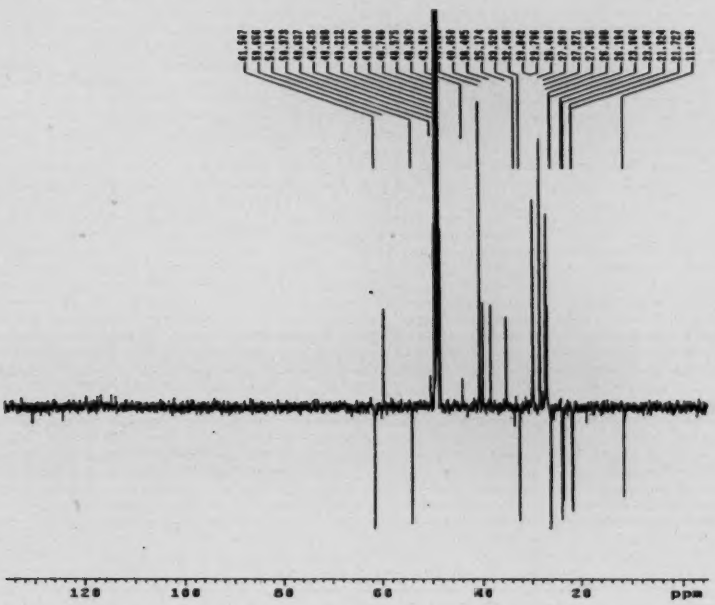
135g



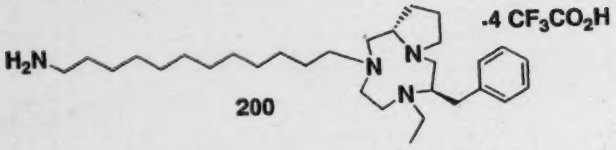
100 MHz ^{13}C NMR in CD_3OD



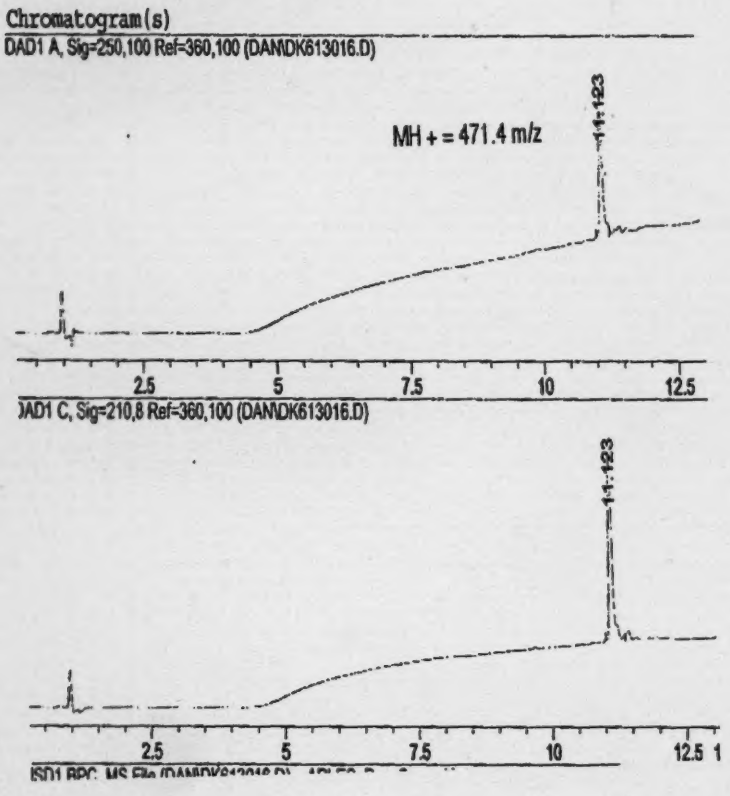
135g



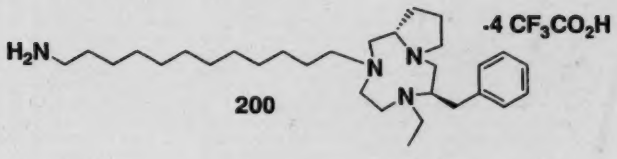
LC-UV of compound 200



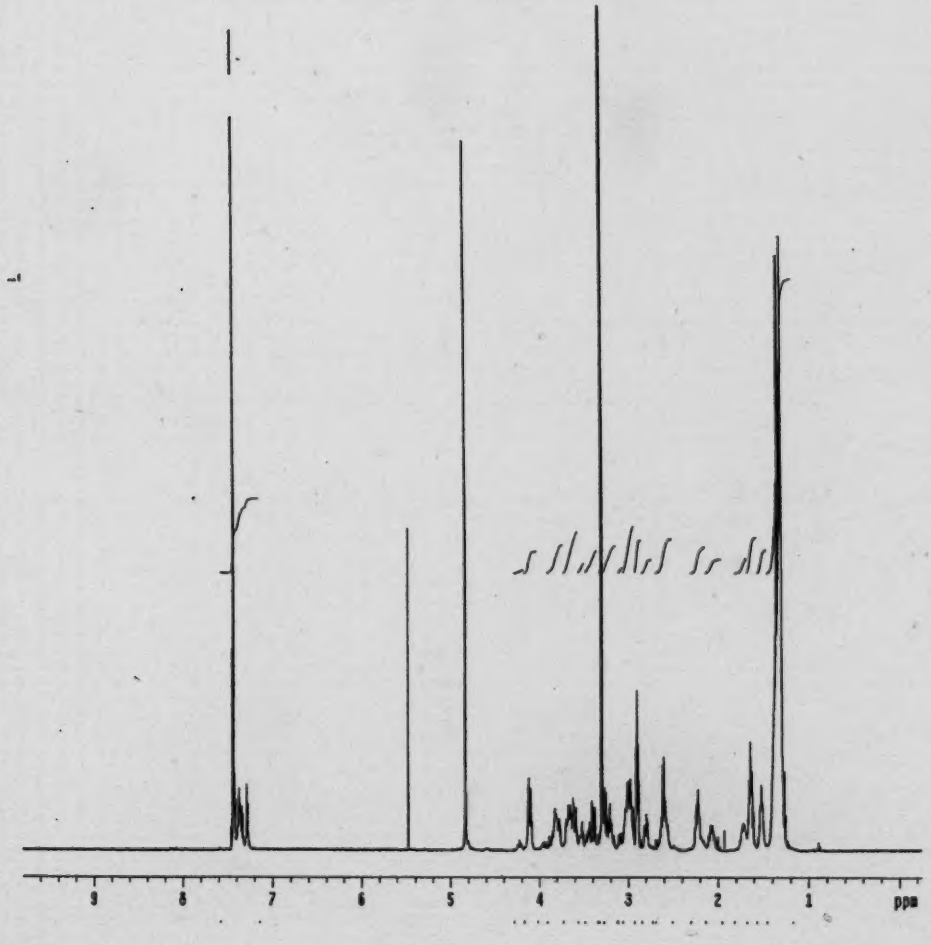
200



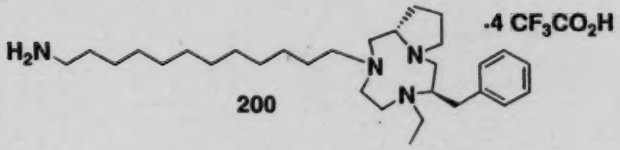
500 MHz ^{1}H NMR in CD_3OD



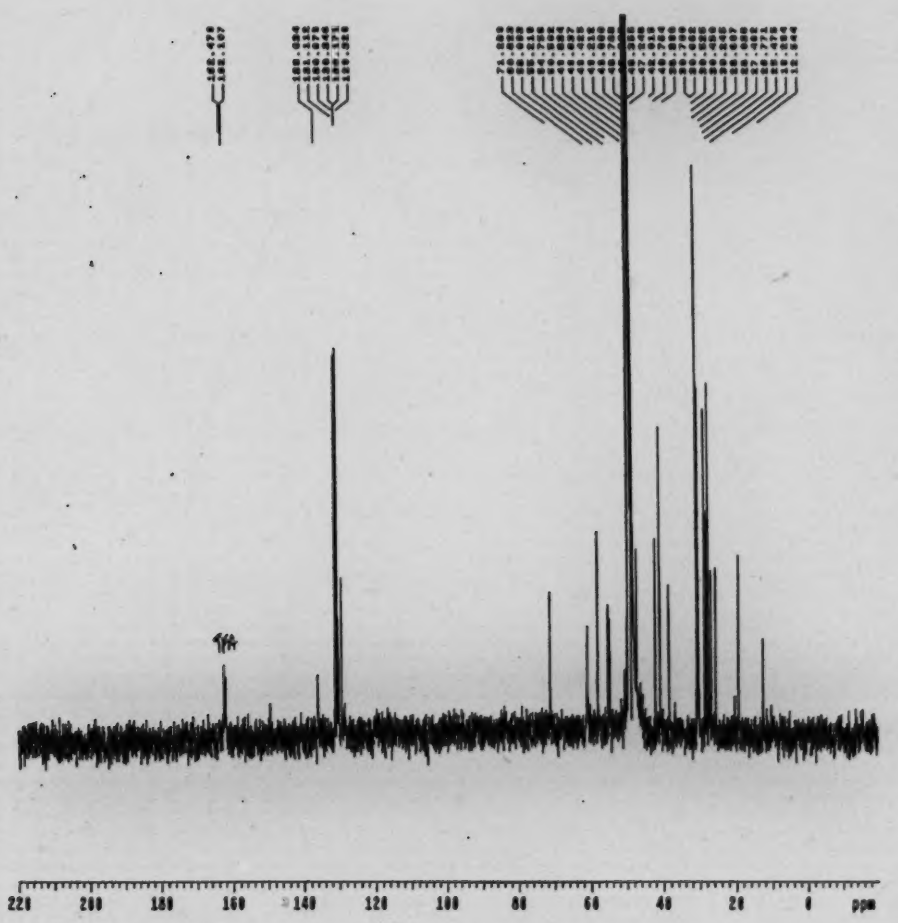
200



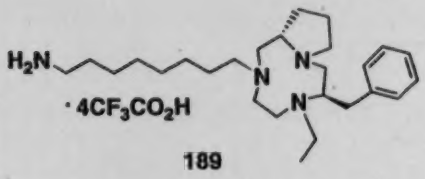
75 MHz ^{13}C NMR in CD_3OD



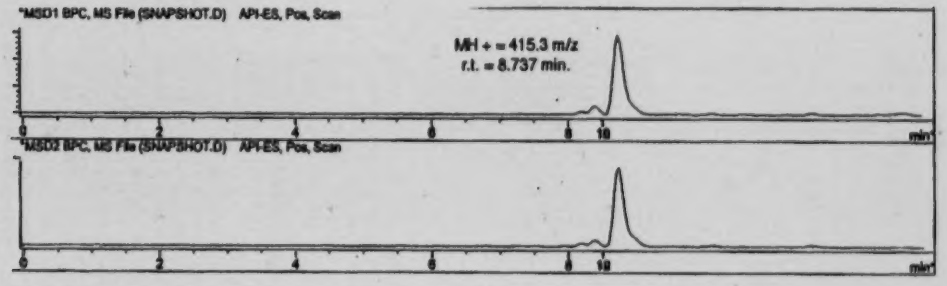
200



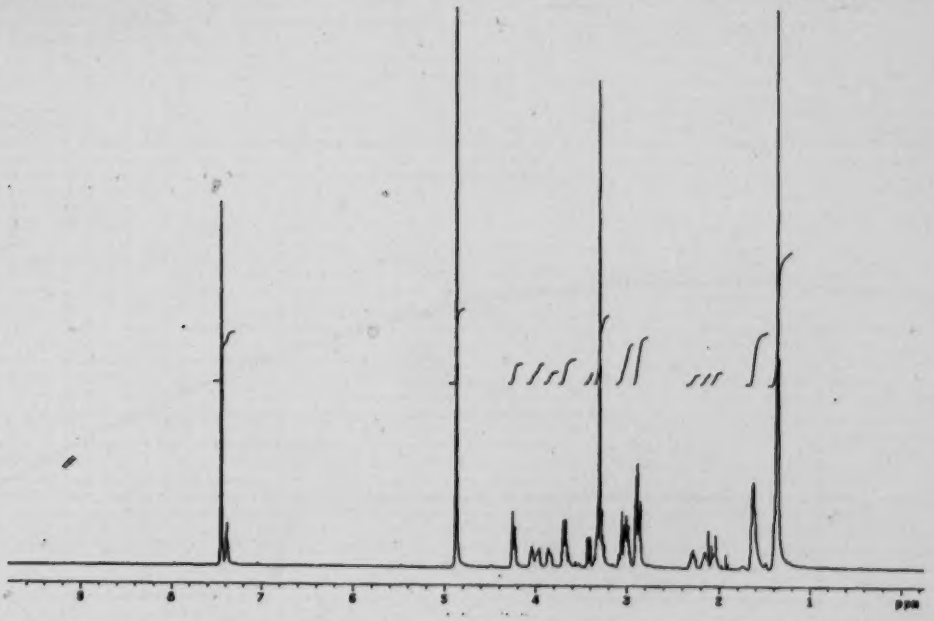
LC-MS of compound 189



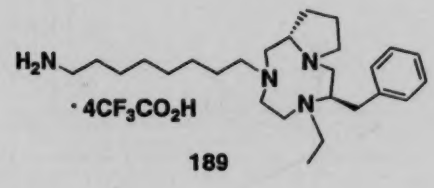
189



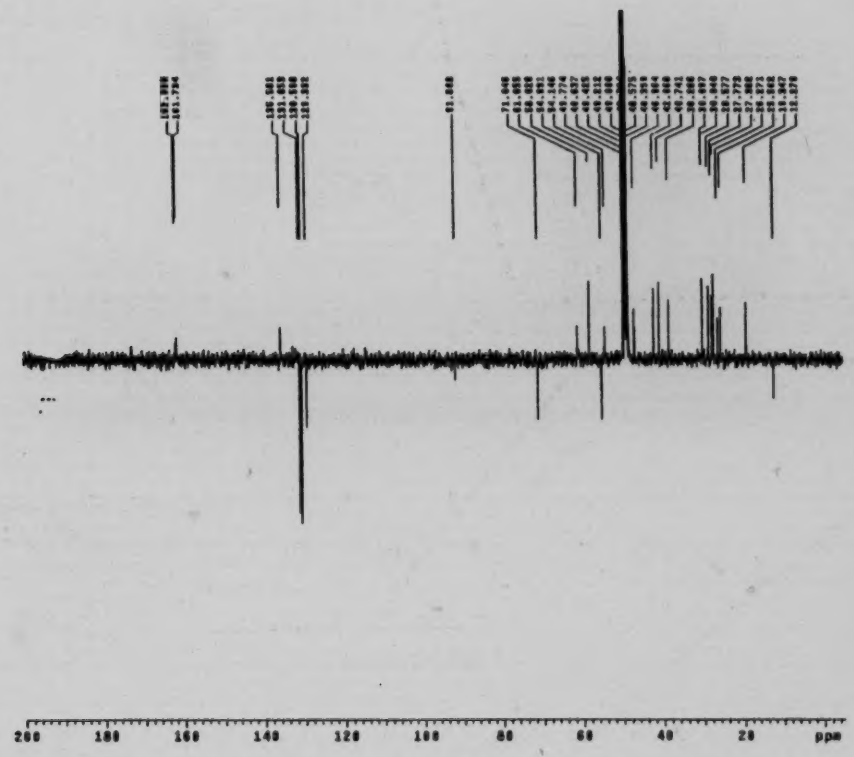
500 MHz ^{1}H NMR



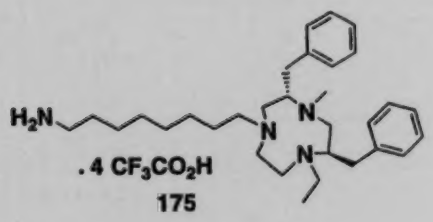
100 MHz ^{13}C NMR (APT) in CD_3OD



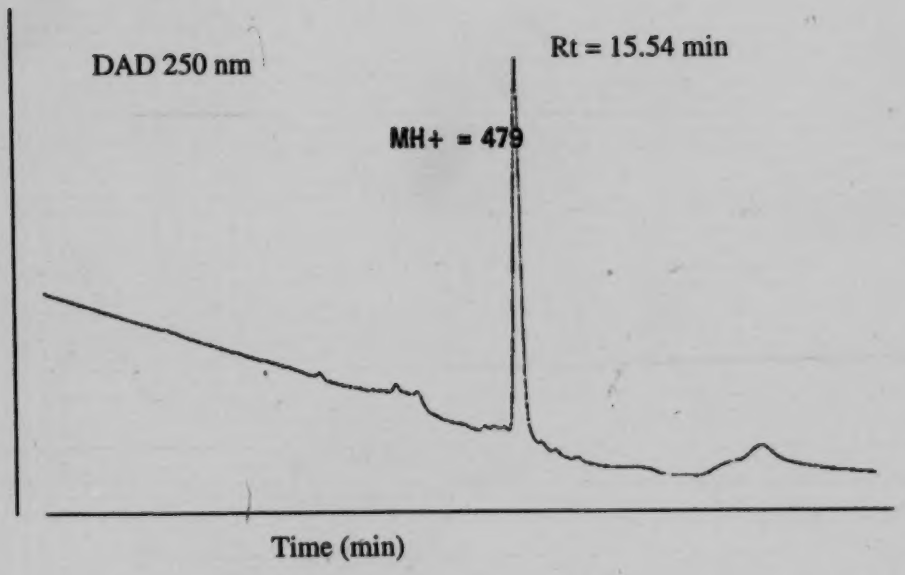
189



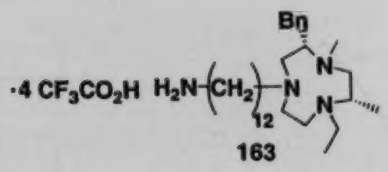
LC-UV of compound 175



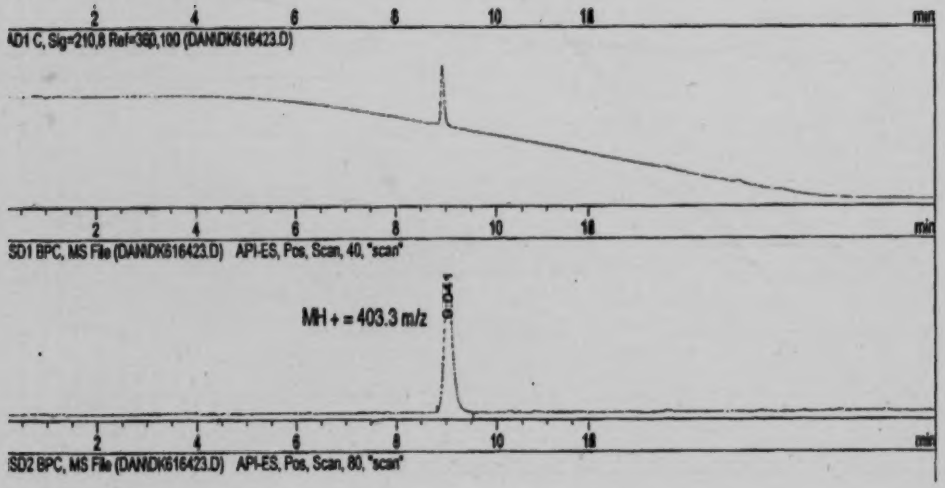
175



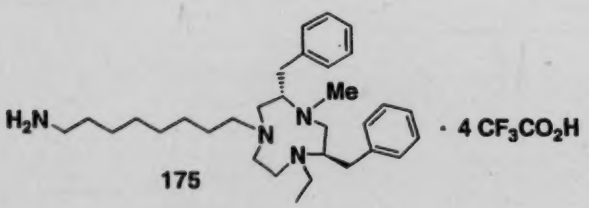
LC-MS of compound 163



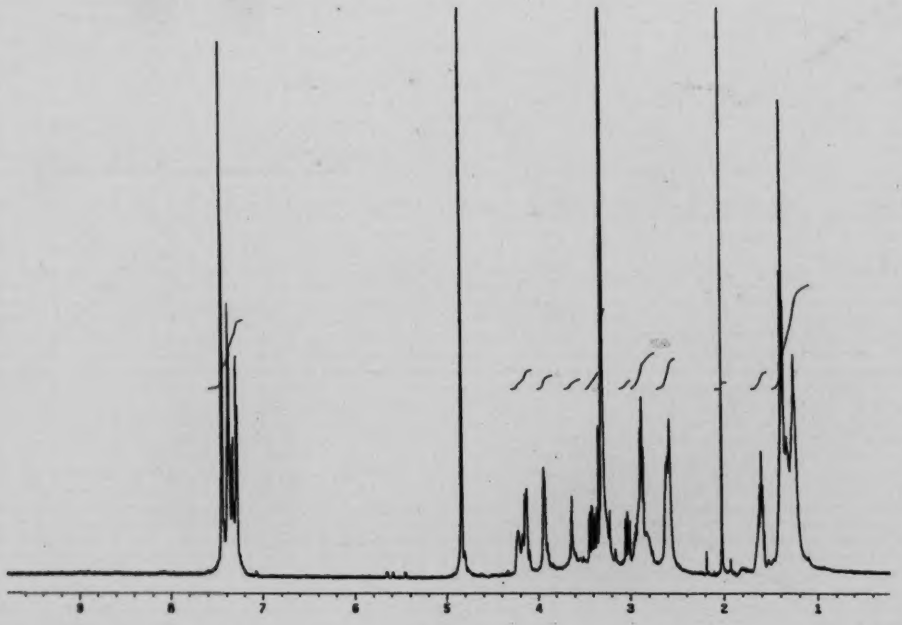
163



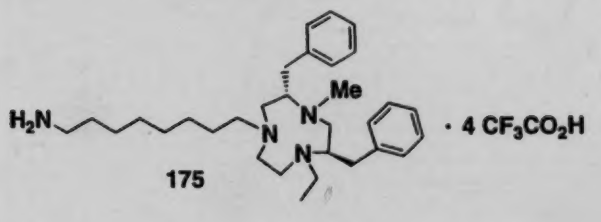
500 MHz ^{1}H NMR in CD_3OD



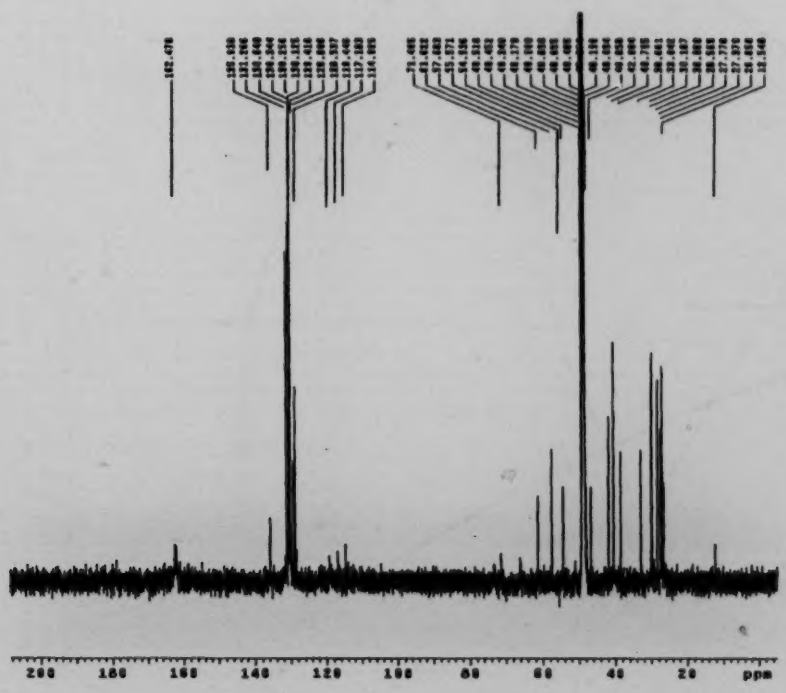
175



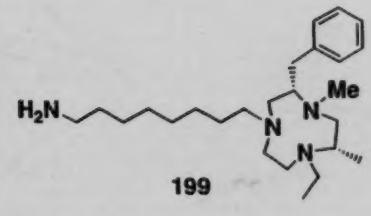
125 MHz ^{13}C NMR in CD_3OD



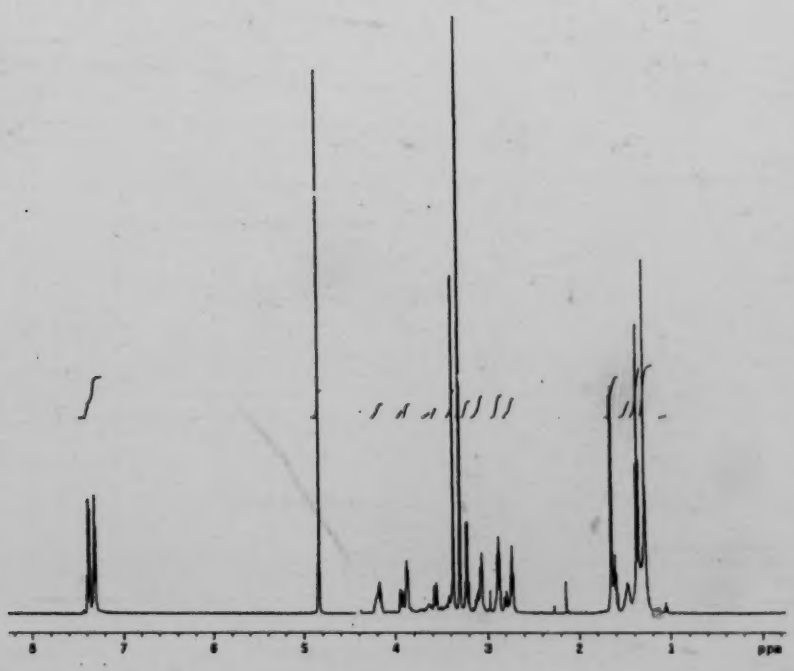
175



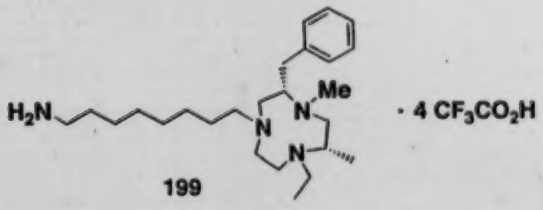
500 MHz ^{1}H NMR in CD_3OD



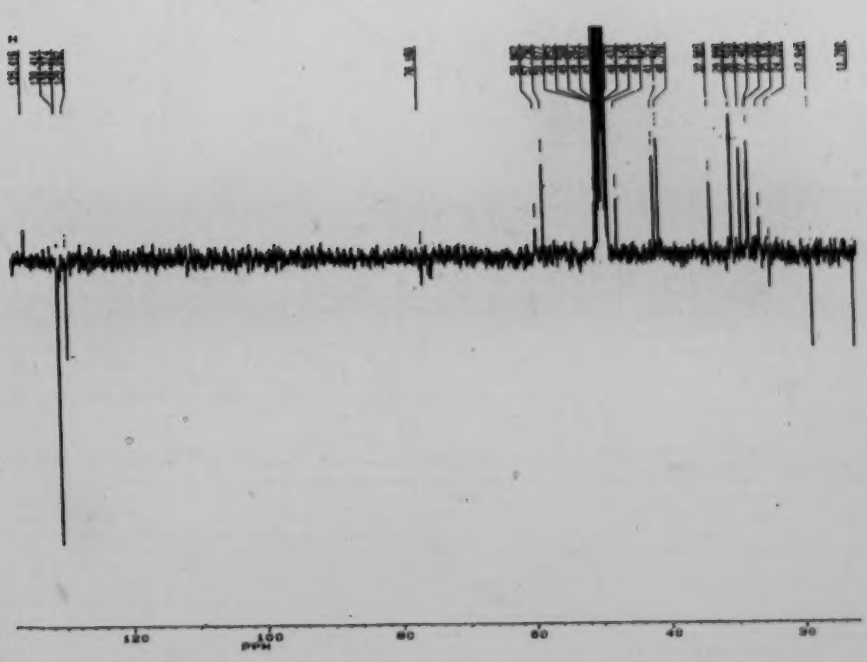
199 · 4 CF_3CO_2H



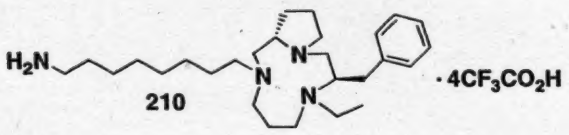
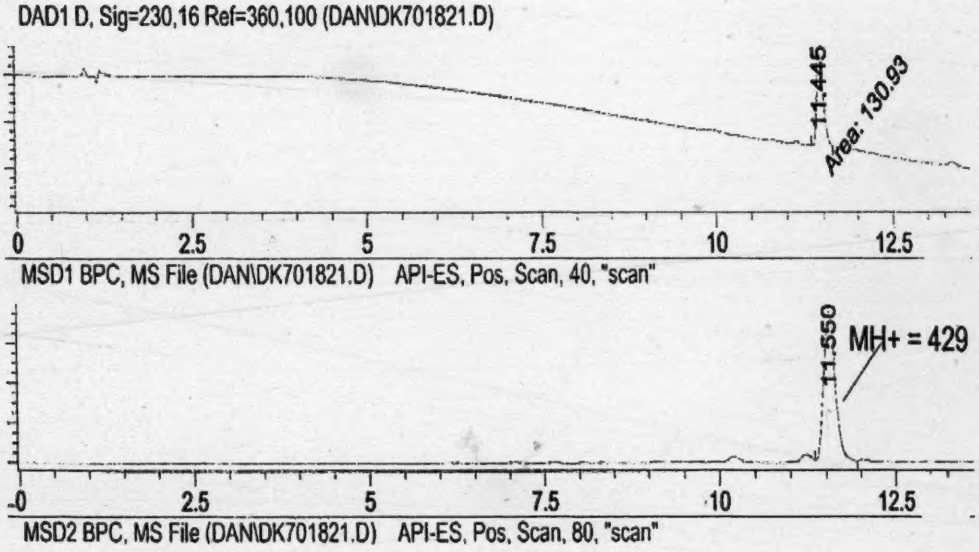
125 MHz ^{13}C NMR in CD_3OD



199



LC-UV and LC-MS of compound 210



210